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PCORI REVIEW AND EVIDENCE VISUALIZATION REPORT

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Drugs and Devices for Migraine Prevention: Interactive Evidence Maps

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Abstract

Background: Migraine headache is a common, disabling condition that impacts 1 in 6 Americans. Although many interventions for migraine prevention have been shown to be effective, decision making for patients and physicians can be complex. Although many newer interventions have received United States (US) Food and Drug Administration (FDA) clearance, no systematic reviews have synthesized evidence for efficacy or harms across old and newer interventions.

Purpose: To summarize evidence from randomized controlled trials (RCTs) for pharmacologic drugs and devices for migraine prevention in visual web-based evidence maps. Specifically, these evidence maps were intended to do the following:

- Visualize all existing evidence from randomized clinical trials on drugs and non-invasive devices for migraine prevention.
- Assess effectiveness of guideline recommended drugs and noninvasive devices for migraine reduction, tolerability, and reported harms.
- Present findings in an easy-to-use interactive visual format.

Methods: The ECRI Evidence-based Practice Center performed a rapid review of the literature to identify existing RCTs for 44 drugs and 2 devices for migraine prevention. We searched PubMed and EMBASE from inception to June 24, 2020. We included English-language RCTs enrolling adults with episodic or chronic migraine, a study duration ≥ 8 weeks, and >10 patients per arm.

For a subset of interventions (15 drugs, 2 devices) we performed meta-analyses of inactive controlled RCTs to assess efficacy and harms. We used the Cochrane risk of bias tool to assess individual studies and Grading and Recommendations Assessment, Development and Evaluation (GRADE) rating system to assess the quality of evidence.

We summarized findings using 3 web-based evidence maps, accessible here: https://www.pcori.org/research-results/evidence-synthesis/evidence-maps-and-evidence-visualizations/drugs-devices-migraine

Results: Overall, 203 RCTs were included: 78 trials in Map 1, 123 trials in Map 2, and 133 trials in Map 3. Two visualizations (Maps 1 and 2) presented findings from placebo-/sham-controlled RCTs, while Map 3 displayed comparisons from head-to-head RCTs.

Key Findings: Placebo-/Sham-Controlled RCTs:

- **Episodic migraine**: Aside from onabotulinumtoxinA (no effect), interventions improved headaches by 0.5 to 2.4 migraine days per month. Efficacy for common first-line interventions (amitriptyline, propranolol, topiramate) was underwhelming (0.73 to 0.95 fewer migraine days per month) and based on low/very-low quality evidence. Calcitonin gene–related peptide (CGRP) antagonists generally provided larger efficacy with fewer side effects and higher quality evidence. Further research is needed to confirm efficacy of devices.
- **Chronic migraine**: Aside from valproate, interventions reduced migraines by 0.9 to 4.2 migraine days per month. Based on 2 small trials, valproate offered a large reduction of 13.2 migraine days per month, although this evidence was rated very low quality.
- **Sparse evidence for tricyclic antidepressants**: Although commonly used as first-line therapy, placebo-controlled RCTs supporting efficacy are sparse (amitriptyline) or nonexistent (nortriptyline).

Key Findings: Head-to-head RCTs:

- **Key evidence gaps:** No direct comparisons of CGRP antagonists or devices to standard migraine prevention therapies exist.

Conclusion: Many interventions reduced migraine, but the clinical importance of these reductions remains unclear. While valproate (an older drug) provided the largest overall migraine reduction, most newer therapies appeared to have comparable efficacy and favorable tolerability. Future work assessing efficacy from head-to-head comparisons is needed to support policy and treatment decisions.

Background

Migraine headache is a common, disabling condition that affected 16% of American adults in 2018; in 2016, migraine accounted for 4 million emergency department visits.[1] Interventions for migraine prevention aim to reduce the number and severity of migraine headaches. Because numerous therapies for migraine prevention therapy exist, selecting a therapy can be challenging. Most pharmacologic therapies commonly used for migraine prevention were originally developed for treatment of other medical conditions, such as hypertension, epilepsy, or depression. Many of these drugs have potential side effects (eg, sedation, hypertension, kidney stones, teratogenicity) that could preclude use in groups of patients, depending on a variety of clinical factors. Thus, choosing a therapy for migraine prevention typically requires careful consideration of patient comorbidities and preferences. Decision making also requires consideration of access: patients are typically required to use older pharmacologic therapies (such as tricyclic antidepressants or beta-blockers) before they are eligible for newer, more costly therapies.

Although many drugs for migraine prevention have been in use for several decades, recently, multiple newer interventions have received FDA clearance, including calcitonin gene–related peptide (CGRP) antagonists and devices (eg, the transcutaneous supraorbital nerve stimulator, noninvasive vagus nerve stimulator). Assessment of the efficacy, tolerability, and side effects of traditional therapies for migraine prevention alongside newer therapies could help inform decisions and identify important evidence gaps.

Scope and Purpose

Migraine prevention therapies encompass a wide range of interventions, including traditional pharmacologic drugs and devices, as well as behavioral therapies, nutritional supplements, and complementary and alternative medicine (CAM) therapies. After considering multiple factors such as existing evidence-based clinical practice guidelines (see Appendix A), anticipated size of evidence base, visual design considerations, and desired timeline, we decided this project would focus on evidence for pharmacologic drugs and devices for migraine prevention.

At the request of the Patient-Centered Outcomes Research Institute (PCORI), ECRI performed a rapid review and conducted meta-analyses to inform creation of 3 web-based interactive evidence maps to present findings using an accessible visual format for clinicians, researchers, and policymakers. In addition, patients may find the maps informative for exploring treatment options. We completed this review on a compressed timeline (in a little more than 6 months) to meet the needs of PCORI stakeholders.

Methods

We performed a rapid review/meta-analysis to address the following 2 key questions for adult patients with episodic or chronic migraine:

Key Question 1: What are the benefits and harms of selected newer drugs and devices (CGRP antagonists and devices) and established pharmacologic therapies (ie, recommended by evidence-based guidelines) for migraine prevention?

Key Question 2: What pharmacologic and noninvasive device interventions for migraine prevention have been assessed using randomized controlled trials (RCTs)?

We designed 3 web-based visual evidence maps to summarize evidence addressing these key questions. Key characteristics of these maps are presented in Table 1.

Table 1. Overview of Map Characteristics

	Key Question 1	Key Question 2	
	Map 1. Benefits and Harms of Selected Interventions for Migraine Prevention: Evidence from Placebo/Sham-Controlled RCTs	**Map 2. What Types of Drugs and Devices have Been Studied with RCTs for Migraine Prevention?**	**Map 3. Head-to-Head Comparisons of Drugs and Devices for Prevention**
Type of RCTs	Placebo/sham controlled	Placebo/sham controlled	Head-to-head comparisons
Criteria for interventions to be displayed in map	All interventions of interest displayed (including those for which no placebo-/sham-controlled RCTs were identified)	Only interventions assessed with placebo-/sham-controlled RCTs displayed	Only interventions assessed with head-to-head RCTs displayed
Summarizes efficacy	Yes	No	No
Key information reported	For each individual intervention, pooled analysis of the following: • Migraine reduction (migraine days per month) • Trial dropout due to adverse events • Adverse events	Number of trials and number of patients randomized displayed by the following: • Type of intervention (ie, drug class) • Individual drugs or devices Number of existing head-to-head comparisons for individual drugs or devices	Number of head-to-head comparisons (including dose comparisons) for individual drugs and devices Study details for each comparison, including author, migraine type, and comparison arms (intervention and subjects per arm)

Table 2 shows included drugs and devices. For Map 1 (assessing effectiveness), we selected 17 interventions of interest. For Maps 2 and 3 (which summarize existing RCTs but do not assess efficacy), we included all interventions included in Map 1, plus 29 additional interventions.

Table 2. Included Interventions by Map

	Key Question 1	Key Question 2	
Intervention Type	**Map 1: Benefits and Harms of Selected Interventions**	**Map 2: Drugs and Devices That Have Been Studied with RCTs**	**Map 3: Head-to-Head Comparisons**
		Additional interventions included	
Angiotensin-converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs)	• Lisinopril • Candesartan	• Captopril • Enalapril • Telmisartan	
Antiepileptics	• Topiramate • Valproic acid	• Gabapentin • Zonisamide • Levetiracetam • Lamotrigine • Oxcarbazepine • Carbamazepine	
Beta-blockers	• Metoprolol • Propranolol	• Atenolol • Nadolol • Timolol • Nebivolol • Bisoprolol • Acebutolol	
Calcitonin gene–related peptide (CGRP) antagonists	• Atogepant • Erenumab • Fremanezumab • Galcanezumab • Eptinezumab	• —	
Botulinum toxin type A	• OnabotulinumtoxinA	• AbobotulinumtoxinA • IncobutulinumtoxinA • Unspecified botulinum toxin type A	
Tricyclic antidepressants	• Amitriptyline • Nortriptyline	• Protriptyline • Clomipramine	

	Key Question 1	Key Question 2	
Intervention Type	**Map 1: Benefits and Harms of Selected Interventions**	**Map 2: Drugs and Devices That Have Been Studied with RCTs**	**Map 3: Head-to-Head Comparisons**
		Additional interventions included	
Other antidepressants	• Venlafaxine	• Fluoxetine • Escitalopram • Fluvoxamine • Citalopram	
Alpha agonists	—	• Clonidine • Guanfacine	
Calcium channel blockers	—	• Verapamil • Nicardipine • Nimodipine • Nifedipine	
Devices	• Transcutaneous supraorbital nerve stimulation (Cefaly) • Noninvasive vagus nerve stimulator (gammaCore)	—	

Stakeholder Input

To inform map content and design, we interviewed key stakeholders including clinicians, patients, policymakers, and primary care physicians (see Acknowledgments). Early input from clinicians and patients informed scope (selection of interventions and outcomes) and map design. Input from policymakers including payers and funders as well as primary care physicians informed data visualization and usability considerations. Our clinician stakeholders were neurologists with expertise in treating migraine headaches and headache research. Our patient stakeholders were women with a personal history of treatment for migraine headaches and experience advocating for and communicating with the migraine community. Finally, the report and evidence maps underwent peer review by our clinician stakeholders and a reviewer with expertise in systematic review and meta-analysis methodology.

Literature Search

A medical information specialist searched PubMed and EMBASE/Medline to identify RCTs for migraine prevention interventions from inception to June 24, 2020. In addition, the specialist searched EMBASE/Medline for relevant systematic reviews through December 16, 2019. Bibliographies from relevant systematic reviews (SRs) were used to identify additional trials. The full search strategy is available in Appendix B.

Inclusion/Exclusion Criteria

We included studies that met the following criteria:

- RCT comparing intervention of interest to placebo/sham (for Map 1/Map 2) or active intervention (Map 3)
- Full-length, English-language published study
- At least one intervention of interest assessed
- Study included >80% patients with migraine (or reported data separately for patients with migraine). We included episodic and/or chronic migraine patients; studies were not required to report outcome separately for episodic/chronic.
- Age ≥ 16
- N ≥ 10 in each study arm at follow-up and reported outcome data for ≥50% of patients enrolled
- Trial duration ≥ 8 weeks

- Study reported at least 1 of the following 5 outcomes for migraine efficacy: migraine days or migraines per month, number of headache days or headaches per month, or 50% reduction in migraine frequency. Studies that did not report any of these outcomes, but reporting related efficacy outcomes (eg, index based on migraine frequency and severity) were excluded from Map 1 but included in Maps 2 or 3.

In addition, for Map 1, if crossover RCTs reported a washout period, we included data for both study periods. To avoid carryover effects, if studies failed to report a washout period (or its length), we included only period 1 data. If period 1 data were *not* reported separately, we excluded the study from Map 1 (but included it in Map 2 or 3, as appropriate).

Screening

We performed dual independent screening for abstracts and full-text articles using DistillerSR (Evidence Partners, Ottawa, Ontario, Canada) with disagreements resolved by a third reviewer. See Appendix C for the flow diagram.

Rapid-Review Methodology

To complete this work in a compressed timeline, we used 2 streamlined rapid-review methods: risk of bias and quality-of-evidence assessments performed by a single analyst with a 10% random check by a second analyst for risk of bias only. In addition, this work differs from typical systematic reviews in that results are primarily presented in the data visualizations, along with this report. However, in other respects, our methods were aligned with standard guidance for systematic reviews.[2, 3]

Data Extraction and Meta-analysis

A single experienced analyst extracted data from full-text articles, with a 10% random validation by another analyst.

We extracted study characteristics including country, year, migraine type, years since onset of migraine, and type of RCT (parallel vs crossover), interventions, comparisons, and number of patients randomized per arm from all included studies. We categorized migraine type as episodic (<15 migraines or headaches per month), chronic (≥15 migraines or headaches per month), episodic plus chronic, and other/not reported. See Appendix D for more details.

Map 1 Outcomes

For studies included in Map 1, we also extracted outcomes for migraine reduction, trial dropout from adverse effects (as a measure of tolerability), and adverse effects. For each outcome, we extracted the data point closest to 8 weeks, 12 weeks, and 6 months, as well as the longest reported timepoint, with data for multiple timepoints extracted if reported.

Specifically, we categorized data from various timepoints as follows:

- 8 weeks: 8 to <12 weeks
- 12 weeks: 12 weeks to <6 months
- 6 months: ≥6 months

Migraine Reduction and Trial Dropout

For migraine reduction, we extracted the following specific outcomes, in descending order of preference:

- Migraine days per month
- Migraines per month
- Headache days per month
- Headaches per month

We also extracted 50% reduction in migraine frequency (migraines or migraine days) if reported.

For trial dropout, we extracted the proportion of patients from each arm who dropped out of trials due to adverse effects.

Efficacy Measures and Minimally Important Difference

One accepted threshold for efficacy for migraine prevention is a 50% reduction in number of migraines per month.[4] However, only roughly half (41 of 78) of studies included in Map 1 reported this outcome, instead reporting results using 1 of the 4 other continuous outcomes of interest (eg, migraine days per month). Ideally, we would have generated a pooled analysis of 50% reduction in migraine/headache frequency by converting these data from continuous outcomes into the dichotomous 50% reduction outcome. However, nearly no studies reported individual before-and-after patient-level data necessary to support meta-analysis of these data across migraine subtypes and multiple end points planned for this map. Thus, we chose to use migraine days per month as the primary outcome measure to display migraine reduction efficacy.

No consensus regarding a minimally important difference (MID) for migraine days per month exists. However, 2 older studies specified a reduction of 1.5 migraines per month as a

"clinically important" difference between groups for migraine reduction.[5, 6] Using the median baselines (for migraines per month and migraine days per month), this corresponds to 2.5 migraine days per month reduction, which we used as the MID for quality-of-evidence assessment.

Meta-analysis

To prepare efficacy data for meta-analysis, we calculated or imputed means and standard deviations (SDs) when not reported. We used Hedges' *g* as the measure of treatment effect for efficacy and relative risk (RR) for withdrawal due to adverse events. For crossover trials that did not report results accounting for the paired nature of the data, we estimated the standardized mean difference and its standard error using a correlation coefficient of 0.5. If only 50% reduction in migraine frequency was reported, we estimated the Hedges' *g* by dividing the log odds ratio by 1.65.[7] These statistical approaches supported inclusion of as much data as possible in our meta-analyses. Studies that reported results of interest, but were not suitable for inclusion in the meta-analyses (despite these approaches), are included in the appropriate hover text in the map.

Before combining different doses of the same treatment within or across trials, we considered whether doses assessed in trials were used in current clinical practice. Based on input from our technical expert panel, we excluded data for eptinezumab 1000 mg from the analysis.

We used random-effects meta-analytic models based on the DerSimonian and Laird method to incorporate between-study heterogeneity.[8] We performed all analyses in Stata 13.[9] We synthesized evidence for efficacy and trial dropout in 230 analyses, of which 129 were meta-analyses.

Adverse Events

To prioritize adverse events for extraction, our 3 technical expert panel (TEP) members independently listed 5 to 7 key adverse effects for each intervention. These key adverse effects were combined to create a list of adverse events for extraction (see Appendix D). If studies did not report individual side effects (eg, dizziness) by study arm, we extracted information regarding serious adverse events or general adverse events.

For each intervention, we calculated pooled RR and absolute risk difference for each adverse effect. We characterized frequency of adverse effects for each intervention by selecting the adverse effect with the *largest* absolute risk difference (between intervention and placebo/sham groups). Based on this difference, we categorized frequency of adverse effects for each intervention as the following:

- 0 to 5%: Rare
- ≥5 to 15%: Infrequent
- ≥15%: More common

This approach flagged an intervention as having "more common" adverse effects if *any* adverse effect had an absolute risk difference of ≥15% for the intervention arm (compared with placebo/sham). For adverse effects (unlike outcomes for efficacy and dropout), we pooled all available data across all migraine types and study durations for each intervention.

For 2 interventions, we noted substantial differences in risk at higher doses. For these 2 interventions (topiramate ≤200 mg vs topiramate >200 mg) and (onabotulinumtoxinA <225 units vs onabotulinumtoxinA ≥225 units), we calculated pooled RR for all combined doses as well as for each dose separately. However, the overall rating (rare, infrequent, or more common) was determined using the absolute risk difference from *combined* doses. For example, onabotulinumtoxinA ≥225 units had an absolute risk difference of 19% and onabotulinumtoxinA <225 units had an absolute risk difference of 14%. However, as their combined absolute risk difference was 14.6%, we categorized frequency of adverse effects as infrequent.

Risk of Bias Assessment

We used the Cochrane risk of bias tool[3] to assess risk of bias for 5 domains: selection bias (randomization and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessors), attrition bias, and reporting bias. All except performance bias and selective outcome reporting bias were considered key domains for rating the overall risk of bias. We piloted assessment of 2 studies and resolved discrepancies. Remaining studies were rated by a single analyst with a 10% check by a second analyst for agreement.

Quality-of-Evidence Assessment

We used GRADE to rate the quality of evidence for migraine efficacy and trial dropout outcomes as high, moderate, low, or very low for each permutation of filters.[10] We piloted assessment of 5 evidence bases across all analysts and resolved discrepancies. Remaining evidence for each outcome was assessed by a single analyst.

To assess study limitations, we used the Cochrane risk of bias tool.[3] To assess indirectness, in addition to typical considerations, we downgraded studies selectively enrolling "enriched" populations (randomizing only patients who had already responded to treatment during a baseline phase). For inconsistency, we examined the forest plot as well as the value of I^2 to judge whether inconsistency was serious. We did not formally assess publication bias because it was not feasible.

To assess imprecision, given the absence of a clear MID for our primary outcome measure (migraine days per month), we used a between-group difference of 1.5 migraines per month cited by 2 studies (as noted above).[5, 6] Using the typical SD for migraine frequency, this difference was equivalent to Hedges' *g* of 0.69. We used this value as an MID to assess the evidence base (summary *g*'s for each meta-analyses), downgrading for imprecision if the confidence interval crossed +0.69 or –0.69. For trial dropout due to adverse effects, we downgraded for imprecision for RR < 0.8 or > 1.25 based on FDA guidance that 0.8 to 1.25 is an appropriate range for therapeutic equivalence of the ratio of plasma drug levels.[11]

Data Visualization

Map data from Microsoft Excel was incorporated into Tableau for data visualization by Lovelytics, a data visualization firm. For Map 1, to enhance clinically interpretability in the visualization, we converted results from *g* to migraine days per month using typical migraine type-specific SDs derived from the data. Similarly, for trial dropout due to adverse effects, we converted RR to risk differences by assuming a 1% rate in the placebo or sham groups. Users can customize the display of data for efficacy and trial dropout using the following filters:

- Migraine type (any, episodic, chronic, other/not reported)
- Study duration (any, 8-11 weeks only, 12-25 weeks, ≥6 months)
- Quality of evidence (high, moderate, low, very low)

We sought and iteratively incorporated feedback on visualization and usability from potential end-users including primary care providers (physicians and nurse practitioner), migraine experts, a payer, guideline developers, and funders (see Acknowledgments).

In addition to efficacy, dropout, and adverse effects, we extracted disease impact outcomes as a measure of quality of life. However, as relatively few RCTs reported this outcome, we chose not to include it in the visualizations.

To ensure accuracy of data translation, we performed a 5% validity check of data points for each outcome (efficacy, dropout, adverse effects) to ensure consistency between visualization and Excel data.

Results

We identified 203 RCTs (published in 254 articles) that met inclusion criteria: 78 trials for Map 1, 123 trials for Map 2, and 133 trials with head-to-head comparisons for Map 3. See Appendix C for a flow diagram. Appendix D provides characteristics of included studies.

Map 1. Benefits and Harms of Selected Interventions for Migraine Prevention: Evidence From Placebo-/Sham-Controlled RCTs

This map summarized 78 placebo or sham-controlled RCTs assessing benefits and harms for 15 drugs and 2 devices. Results and links to individual studies can be viewed using the map, here. Below, we summarize key findings.

Of interventions included in Map 1, we identified the largest number of trials for CGRP antagonists (22 RCTs), followed by antiepileptics (20 trials), and botulinum toxin type A (17 trials). Only 2 trials assessed devices (noninvasive vagal nerve stimulation [1 RCT] and transcutaneous supraorbital nerve stimulation [1 RCT]). Similarly, only a single RCT respectively assessed lisinopril and atogepant. No trials assessed nortriptyline. Most trials (83%) were published after 2000. Older trials (published before 2000) assessed valproate (n = 3), propranolol (n = 9), and metoprolol (n = 2).

Overall, the median baseline number of migraine days per month for study participants across included trials was 9 (any migraine type), 8 (episodic migraine), and 18 (chronic migraine).

Efficacy for All Migraine Types

The efficacy of interventions considering data for all migraine types and follow-up durations ranged from 0.56 to 3.4 fewer migraine days per month (forest plots for each intervention are included in Appendix E.) Overall, valproate offered the largest reduction: pooled analysis of 7 trials[12-18] found valproate provided 3.4 fewer migraine days per month, although the quality of evidence was low. Patients receiving valproate were more likely to drop out of trials due to adverse effects (RR 1.7; 95% CI, 0.7-4.2). However, the *absolute* risk of dropping out remained relatively low (1.9% vs 1% for valproate vs placebo), and adverse effects were rare. Compared with placebo, valproate was slightly more likely to cause weight gain (5% risk difference [RD]), dizziness (4% RD), and fatigue (4% RD).

Only 6 (of 17) interventions represented in Map 1 had high-quality evidence for efficacy: the 5 CGRP antagonists (atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab), and noninvasive vagal nerve stimulation. Efficacy for CGRP antagonists ranged from 1.4 to 1.9 fewer migraine days per month compared with placebo, while noninvasive vagal nerve stimulation had the smallest effect size (only 0.56 fewer migraine days per month compared with sham stimulation). An additional 5 interventions had moderate-quality evidence for efficacy: amitriptyline, candesartan, metoprolol, propranolol, and onabotulinumtoxinA.

Episodic Migraine

Fifty trials specifically assessed efficacy for episodic migraine (select "episodic migraine" filter on the left-hand side of the visual). Topiramate and propranolol each had 8 trials, followed by onabotulinumtoxinA and galcanezumab (6 trials each), erenumab (5 trials), valproate (4 trials), metoprolol, fremanezumab, and amitriptyline (2 trials each), and lisinopril, atogepant, eptinezumab, and venlafaxine, and the 2 devices (1 trial each).

Venlafaxine, transcutaneous supraorbital nerve stimulation (Cefaly), and valproate offered the highest efficacy (2 to 2.4 fewer migraine days per month compared with placebo). While effect sizes were slightly larger for venlafaxine and Cefaly, each was supported by only a single RCT[19, 20] enrolling fewer than 70 patients (compared with 4 trials for valproate). Notably, venlafaxine was not well tolerated: patients randomized to venlafaxine were more likely to drop out due to adverse events (5.6% RD) and reported higher rates of nausea (16% RD), insomnia (9% RD), and fatigue (3% RD) compared with placebo. Cefaly and valproate were better tolerated with rare adverse effects and low trial dropout.

Efficacy for topiramate, propranolol, and amitriptyline (drugs widely used for migraine prevention) ranged from 0.7 to 0.9 fewer migraine days per month (compared with placebo). However, adverse effects were more common in patients using these drugs. For example, compared with placebo, the proportion of patients who reported dry mouth and somnolence was >20% higher for those taking amitriptyline.

High-quality evidence supported 2 treatments (galcanezumab, erenumab) for episodic migraine at all timepoints, including 6 months, although the magnitude of improvement could be considered relatively modest (1.85 fewer migraine days per month or less; see Table 3).

Table 3: Episodic Migraine—High Quality Evidence for Efficacy by Trial Duration[a]

Intervention (No. of Trials)	8 weeks	12 weeks	6 months
Galcanezumab (n = 6)	1.44 migraine days/month	1.83 migraine days/month	1.85 migraine days/month
Erenumab (n = 5)	1.40 migraine days/month	1.22 migraine days/month	1.84 migraine days/month
Fremanezumab (n = 2)	—	1.35 migraine days/month	—
Atogepant (n = 1)	—	1.24 migraine days/month	—
Noninvasive vagal nerve stimulation (gammaCore) (n = 1)	—	0.48 migraine days/month	—

[a] These high-quality evidence ratings occurred when selecting the following map filters: "episodic" for migraine; "high" for quality of evidence; and 8, 12, or 6 months for follow-up.

Chronic Migraine

Fourteen trials specifically assessed efficacy for chronic migraine (select "chronic migraine" filter on the left-hand side of the visual). OnabotulinumtoxinA had the most trials (n = 4), followed by valproate, topiramate, fremanezumab, and galcanezumab (2 trials each). The remaining interventions (amitriptyline, eptinezumab, erenumab) had been assessed with only a single trial.

Valproate offered by far the largest reduction, with 13.2 fewer migraine days per month (pooled data from 2 small trials, very-low-quality evidence),[12, 18] followed by onabotulinumtoxinA, with 3 fewer migraine days per month, and 3 CGRP antagonists (eptinezumab, erenumab, galcanezumab), which offered reductions of about 2.6 migraine days per month. Of note, evidence for valproate was based on 2 small, non-US trials performed in Turkey[18] and Iran[12] that randomized only a combined 52 patients to valproate.

Only a single intervention reported outcomes for chronic migraine patients at 6 months: onabotulinumtoxinA improved migraines by 2.3 migraine days per month, although quality of evidence was low.[21] Only 4 interventions (galcanezumab, fremanezumab, erenumab, eptinezumab) had high-quality evidence supporting efficacy that ranged from 1.7 to 3 fewer migraine days per month (see Table 4).

Table 4: Chronic Migraine—High Quality Evidence for Efficacy by Trial Duration[a]

Intervention (No. of Trials)	8 weeks	12 weeks	6 months
Galcanezumab (n = 2)	1.75 migraine days/month	—	—
Fremanezumab (n = 2)	1.66 migraine days/month	1.58 migraine days/month	—
Erenumab (n = 1)	3.03 migraine days/month	2.65 migraine days/month	—
Eptinezumab (n = 1)	—	2.69 migraine days/month	—

[a] These high-quality evidence ratings occurred when selecting the following map filters: "episodic" for migraine; "high" for quality of evidence; and 8, 12, or 6 months for follow-up.

Tolerability (Trial Dropout and Adverse Effects)

Interventions with the highest relative risk of trial dropout due to adverse events were venlafaxine and onabotulinumtoxinA. (Of note, data for venlafaxine were drawn from only a single, relatively small study of 60 patients.) Conversely, the 2 devices and atogepant had the lowest relative risks of dropout (RR 0.2 to 1). For noninvasive vagal nerve stimulation (gammaCore), patients receiving sham were *more likely* to drop out than those receiving gammaCore.

The frequency of adverse effects was categorized as more common for 5 interventions (candesartan, topiramate, propranolol, venlafaxine, amitriptyline), infrequent for 4 interventions (lisinopril, metoprolol, onabotulinumtoxinA, galcanezumab), and rare for 7 interventions (valproate, atogepant, eptinezumab, erenumab, fremanezumab, noninvasive vagal nerve stimulation, transcutaneous supraorbital nerve stimulation).

Map 2. What Types of Drugs and Devices Have Been Studied With RCTs for Migraine Prevention?

This map summarized 123 placebo or sham controlled RCTs assessing 46 interventions (17 of these interventions are also summarized in Map 1; 29 additional interventions are included in Map 2). Interventions with the largest volume of evidence were the following:

- Antiepileptics: 26 trials, 2859 patients
- Beta-blockers: 25 trials, 1543 patients
- CGRP antagonists: 23 trials, 9317 patients
- Botulinum toxin type A: 19 trials, 2878 patients

Remaining intervention categories had been studied with only <10 RCTs. Notably, although antiepileptics and beta-blockers had more RCTs, CGRP antagonist trials had more than 3 times as many patients randomized compared with antiepileptics.

Map 3. Head-to-Head Comparisons of Drugs and Devices for Migraine Prevention

This map displays existing head-to-head comparisons from 133 RCTs and highlights potential evidence gaps. Overall, included studies captured 207 head-to-head comparisons, of which 42% (n = 86) compared different doses of the same drug. (Users can hide dose comparison trials by selecting the "Hide Dose Comparison Trials" filter on the bottom left-hand side of the visual.)

Not surprisingly, older interventions widely considered effective for migraine prevention (topiramate, valproate, propranolol, botulinum toxin type A, amitriptyline) were the most frequently assessed in head-to-head comparisons, often compared against each other. Notably, the map demonstrates that several of these interventions have also been compared against nutraceuticals (melatonin, riboflavin) and CAM such as acupressure, acupuncture, exercise, and relaxation. (Users can view these by hovering over dots in the "Other" column.)

Map 3 reveals 2 important evidence gaps. Both CGRP antagonists and transcutaneous supraorbital stimulation performed well for migraine reduction in placebo- or sham-controlled trials (as demonstrated in Map 1) with relatively few side effects. No head-to-head trials comparing these interventions against older, commonly used pharmacologic interventions for migraine prevention exist. In fact, CGRP antagonists have not been compared against any other interventions, and only a single trial[22] compared transcutaneous supraorbital stimulation to another type of electrical stimulation (a nonstandard treatment). Direct comparisons of these newer interventions against older therapies to confirm relative efficacy is needed to support decisions by payers, policymakers, and shared decision-making between doctors and patients. Also, comparative effectiveness trials have primarily focused on episodic migraine; only 19 head-to-head comparisons (including 8 dose comparison trials) for chronic migraine exist. However, we note that most of these trials were performed in the past 10 years, which could suggest increased interest in addressing this evidence gap.

Discussion

To our knowledge, this work represents the first rapid review/meta-analysis to assess efficacy for many traditional pharmacologic interventions along with newer drugs and devices. Our analyses confirm that multiple interventions are effective for migraine reduction compared with placebo/sham. As evident in Map 1, older interventions in common use and recommended by guidelines[23, 24] (eg, propranolol, topiramate, valproate, amitriptyline, candesartan) were effective. However, aside from valproate, the size of migraine reduction offered by several newer therapies (CGRP antagonists, transcutaneous supraorbital stimulation) was roughly comparable or slightly larger, but with fewer side effects and dropouts from adverse effects. Of all therapies used for migraine prevention, valproate demonstrated the largest migraine reduction: pooled analysis of 7 trials[12-18] found a reduction of 3.4 migraine days per month, although this evidence was rated low quality. Specifically, valproate provided a large reduction for chronic migraine (13.2 migraine days per month) and smaller effect for episodic migraine (2 migraine days per month).

Important evidence gaps are clear from Map 1. First, few trials reported outcomes beyond 12 weeks, and only 7 interventions had 6-month outcomes. Second, all drugs and devices captured in Map 1 (except for nortriptyline) demonstrated some degree of efficacy for reducing migraines (as anticipated since drugs or devices in common use or recommended in guidelines were intentionally prioritized for inclusion). However, only 6 interventions (of which 5 were CGRP antagonists) were supported by high-quality evidence. For included interventions recommended as first line by an evidence-based practice guideline,[23, 24] overall quality of evidence was only moderate (propranolol, metoprolol), low (valproate), or very low (topiramate). In general, many of these studies were older and had higher risk of bias for many reasons, including poor randomization, unclear blinding procedures, or high attrition. The evidence base for other recommended drugs was quite small: amitriptyline and candesartan were each supported by only 2 trials, and venlafaxine and lisinopril were each supported by only 1.

For most interventions (including CGRP antagonists), the magnitude of improvement was underwhelming. For instance, for included trials of episodic migraine, the baseline median number of migraine days per month was 8. Efficacy for 8 of 9 interventions supported by more than a single RCT ranged from 0.73 to 1.95 fewer migraine days per month (the ninth intervention, onabotulinumtoxinA, is not recommended for episodic migraine). Furthermore, adverse effects were more common for 3 of these interventions (topiramate, amitriptyline, propranolol).

Patients are typically required to start with older drugs (such as propranolol, amitriptyline, or nortriptyline) with failure of several classes of traditional drugs (eg, antihypertensives, antidepressants, antiepileptics) before they are eligible to receive newer, more costly drugs such as CGRP antagonists. Our work highlights the sparse evidence for drugs

commonly used first line (particularly amitriptyline and nortriptyline) and suggests patients could experience fewer side effects if CGRP antagonists were considered for initial therapy, although policymakers would also need to consider the uncertainty regarding long-term side effects and substantively higher cost.

Selecting a migraine prevention therapy requires shared decision making that considers multiple factors, including benefits and harms, patient comorbidities, cost/coverage, and (for women) childbearing potential. Patients often inquire at length about potential side effects; investment in visual evidence maps such as these, which display data on adverse effects alongside efficacy, may support realistic expectations for physicians and patients as they weigh potential tradeoffs.

Limitations

We note several important limitations. First, we used migraine days per month, an accepted measure, as the primary efficacy outcome for meta-analyses. We found that most interventions reduced migraine days per month by fewer than 3. However, because this measure averages effects across all patients, some patients may have experienced greater reductions while others had no change. An alternative measure of efficacy, such as 50% reduction in migraine frequency, may reveal which treatments are likely to provide greater reductions for some patients, even if overall average effects are modest.

As previously noted, inconsistencies in reporting did not allow us to calculate 50% reduction in migraine frequency across all studies. However, we extracted these data whenever reported (see Appendix F, also available by selecting a blue bar in Map 1, and the hyperlink "Data on 50% reduction in migraines or migraine days per month" which appears in the hover). We note that these studies generally defined 50% reduction as a truly successful response, not necessarily an MID (the smallest between-group difference needed to be considered important). Furthermore, it is unclear if patients would consider improving from 20 to 10 migraines a month as equally beneficial as improving from 8 to 4 migraines a month. Although quality-of-life measures (eg, disease impact scores) could help address this question, we found that few studies reported disease impact scores. Thus, while potentially informative, we did not incorporate disease impact scores into the evidence map.

For adverse effect frequency (in Map 1), we extracted only selected adverse effects our clinical experts identified as important for clinical decision making (see Appendix G) and compared reported frequency for intervention and placebo arms. However, in some cases, these estimates could fail to capture side effects important to patients (such as teratogenicity). Many migraine prevention therapies are drugs primarily used for other medical conditions, such as hypertension, depression, or epilepsy. For example, valproate and topiramate have known potential teratogenic side effects from the epilepsy literature; however, no migraine trials reported teratogenicity, since studies of valproate or topiramate excluded women of child-

bearing age due to this already known side effect. These concerns would also be relevant to other interventions with known teratogenicity, such as candesartan and lisinopril. We also note that, although CGRP antagonists appear to have generally favorable side effect profiles, as new drugs, their long-term safety remains unknown.[25]

Given variability in study inclusion criteria across studies, it was not feasible to consider all factors that could have impacted efficacy (such as enrolling only patients who had failed a certain number of prior medications). However, this could have led to underestimation of true efficacy in some cases. Similarly, we did not perform subanalyses based on patient clinical characteristics (eg, number of drugs failed, concurrent headache therapies) and demographics (age or gender) to identify particular patient groups more likely to respond.

In some cases, there may appear to be incongruities between reported findings for efficacy from individual studies and those presented in the visualization (eg, a study reporting no statistically significant difference between intervention and control, but the visualization indicating there is). These differences may be due to differences between the analytic approach taken by trial investigators compared with our approach. To facilitate pooling of data across studies, we focused on group-level means and SDs reported by trials; investigators may have used other approaches to derive *P* values. For example, Schoenen 2013[19] used the Mann-Whitney U test to assess the distributions of migraine days per month for supraorbital transcutaneous nerve stimulation compared with sham and found no statistically significant difference. On the other hand, when directly comparing the means of each group, there is a significant difference.

We included all RCTs regardless of publication date, recognizing that many migraine prevention trials were published as early as the 1980s. However, as expected for an evidence base spanning nearly 4 decades, findings from older trials could be less generalizable today. Older studies were often assessed as high risk of bias due to failure to report methods for randomization or allocation concealment. In fact, randomization method was unclear for 100% of studies published prior to 2000 (n = 13). However, we acknowledge that reporting standards in the past were different, and, in some cases, authors may simply have failed to report the method due to different expectations for reporting at the time.

Finally, some users may primarily be interested in evaluating how interventions perform relative to each other (instead of efficacy compared with placebo/sham). However, Map 1 provides limited utility to evaluate comparative effectiveness. While users could attempt to extrapolate the relative effects by, for example, subtracting the effect of one intervention from another, this could lead to erroneous conclusions. Strong assumptions regarding the similarity of trials are necessary to ensure these indirect comparisons are valid, and we did not formally assess these assumptions, as would be done in a network meta-analysis.[26]

Future Directions

Our work suggests CGRP antagonists offer similar efficacy to many commonly used drugs for migraine prevention with higher tolerability, although long-term safety remains unknown. Future studies reporting on long-term side effects will be important to better inform discussions of risk and benefits and support clinical decision making. Although only assessed with a single smaller RCT, transcutaneous supraorbital nerve stimulation also showed promise for episodic migraine, with significant reduction in migraine days per month and high tolerability. Further trials to confirm efficacy are needed.

As noted, patients often begin therapy with older drug therapies. Head-to-head comparisons of both CGRP antagonists and transcutaneous supraorbital nerve stimulation against other traditional migraine prevention drugs could inform policymakers, particularly given the current higher cost of CRGP antagonists.

More research is needed to confirm efficacy for interventions specific for chronic migraine. Also, although not addressed by this project, many patients express preferences for nonpharmacologic drugs (ie, vitamins or supplements), CAM therapies, devices, or behavioral therapies given perceived lower risk of side effects. Although this work did not assess efficacy of these interventions, head-to-head trials with comparisons against standard pharmacologic drugs exist. Future studies assessing effectiveness and comparative effectiveness of these interventions compared with traditional pharmacologic therapies and devices could inform treatment decisions for patients interested in nonpharmacologic treatments.

Conclusion

Multiple drugs and devices successfully reduced migraines, although the magnitude of migraine reduction for many interventions was not large. Valproate offered the largest reduction in migraine days per month, particularly for chronic migraine sufferers, although this evidence was low or very low quality. Compared with older, traditional drug interventions (except valproate), newer therapies (including CGRP antagonists and transcutaneous supraorbital nerve stimulation) had generally comparable or slightly larger effects with fewer side effects. However, only CGRP antagonists and one device were supported by high-quality evidence for efficacy and few studies assessed outcomes beyond 12 weeks.

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Appendix A. Interventions for Inclusion

Table A-1. Migraine Prevention Interventions Considered for Map 1 (Benefits and Harms of Migraine Prevention Treatments)

Interventions	Included (Yes/No)	Comment
Pharmacologic		
Angiotensin converting enzyme (ACE) inhibitors/Angiotensin receptor blockers (ARBs) (lisinopril, candesartan)	Yes	Scoping suggests evidence for efficacy for lisinopril and candesartan (probably and possibly effective, American Academy of Neurology [AAN]/American Headache Society [AHS] guideline). Commonly used medications for hypertension; included in Table 1
ACE inhibitors/ARBs (captopril, enalapril, telmisartan)	No	Telmisartan considered possibly ineffective by AAN/AHS guideline; captopril and enalapril without significant efficacy in existing systematic review (SR) (Jackson 2015[27])
Alpha-agonists (clonidine, guanfacine)	No	Considered possibly effective by AAN/AHS, but not an emerging therapy, not in common use for migraine
Antithrombotics (acenocoumarol, coumadin, picotamide)	No	Conflicting/inadequate evidence as per AAN/AHS guideline; not in clinical use
Beta-blockers (metoprolol, propranolol)	Yes	Metoprolol, propranolol included as "effective" recommendations in AAN/AHS, propranolol recommended by Scottish Intercollegiate Guidelines Network (SIGN) guideline; included in Table 1
Beta-blockers (timolol)	No	Timolol listed as "effective" in AAN/AHS, but not widely used in clinical practice; also found to be equivalent to metoprolol in recent SR (Jackson 2019[28])
Beta-blockers (atenolol, nadolol, nebivolol, pindolol, bisoprolol)	No	Listed as probably or possibly effective in AAN/AHS, but already evaluated along with other beta-blockers in recent SR (Jackson 2019[28])
Beta-blockers (acebutolol)	No	Considered possibly ineffective as per AAN/AHS guideline
Botox (onabotulinumtoxinA)	Yes	"Recommended" in SIGN and recent AAN guideline for chronic migraine; scoping suggests some evidence for efficacy; included in Table 1

Interventions	Included (Yes/No)	Comment
Pharmacologic		
Calcium channel blockers (nicardipine, nifedipine, nimodipine, verapamil)	No	Listed as inadequate and conflicting evidence by AAN/AHS guideline and not an emerging therapy; scoping suggests many trials, so including could also present feasibility challenge. Evaluated in existing SR (Jackson 2015[27])
Calcitonin gene–related peptide antagonists (erenumab, fremanezumab, galcanezumab, eptinezumab, atogepant)	Yes	Considered an emerging therapy; scoping suggests some evidence for efficacy and interventions of interest to patients; included in Table 1
Cyclandelate	No	Conflicting, inadequate evidence as per AAN/AHS and not in clinical use
Frovatriptan	No	Listed as "effective" by AAN/AHS but only for short-term menstrual migraine prevention (not a focus of this product)
Gabapentin	No	Not recommended by either AAN/AHS or SIGN guidelines) and not an emerging therapy
Nabumetone	No	Possibly ineffective as per AAH/AHS guideline
Naratriptan, zolmitriptan	No	Possibly effective according to AAN/AHS, but only for short-term menstrual migraine prevention, which is not a focus of this product; also not an emerging therapy
Other antidepressants (fluoxetine, fluvoxamine, protriptyline, clomipramine)	No	Listed as conflicting/probably ineffective by AAN/AHS and not an emerging therapy
Other antiepileptics (acetazolamide, carbamazepine, clonazepam, lamotrigine, levetiracetam, oxcarbazepine, vigabatrin, zonisamide)	No	Carbamazepine is possibly effective, but not in common use; other drugs are not listed as effective or probably effective and also are not in common use for migraine
Topiramate	Yes	"Effective" recommendation in AAN/AHS and SIGN guideline; included in Table 1
Tricyclics (amitriptyline, nortriptyline)	Yes	Amitriptyline considered "probably effective" by AAN/AHS and SIGN; nortriptyline recommended for inclusion by clinician stakeholders and in common use; included in Table 1
Valproic acid	Yes	Considered effective by AAN/AHS and SIGN guidelines; included in Table 1
Venlafaxine	Yes	Considered "probably effective" by AAN/AHS and SIGN; recommended for inclusion by clinician stakeholders; included in Table 1

Interventions	Included (Yes/No)	Comment
Devices		
Noninvasive vagus nerve stimulator (gammaCore)	Yes	Intervention of interest for PCORI along with clinicians and patient stakeholders; commonly used in clinical practice; scoping suggests some data; included in Table 1
Supraorbital nerve stimulator (Cefaly)	Yes	Intervention of interest for clinicians and patient stakeholders; commonly used in clinical practice; scoping suggests sparse data (only a single RCT); included in Table 1
Transcranial magnetic stimulation	No	Not in common use and not available to most patients; scoping suggests limited evidence

[a] Interventions in italics are included in Map 1 (Benefits and Harms). Of note, supplements/nutraceuticals, behavioral therapies, and complementary and alternative medicine therapies were considered out of scope for this product.

Table A-2. Recommended Interventions from Guidelines

American Academy of Neurology/American Headache Society		Scottish Intercollegiate Guideline Network[a]		Canadian Headache Society	
Evidence-Based Guideline Update: Pharmacologic Treatment for Episodic Migraine Prevention in Adults (2012; reaffirmed 2015)		**Pharmacological Management of Migraine (2018)**		**Guideline for Migraine Prophylaxis (2012)**	
Effective	Anti-epileptic drugs (divalproex, sodium valproate, topiramate), beta-blockers (metoprolol, propranolol, timolol), triptans (frovatriptan for short-term menstrual migraine prevention)	Recommended	Propranolol (60 to 180 mg), topiramate; botox (for chronic migraine only)	Strong recommendation (high quality of evidence)	Topiramate, propranolol, metoprolol, amitriptyline
Probably effective	Antidepressants (amitriptyline, venlafaxine), beta-blockers (atenolol, nadolol), triptans (naratriptan, zolmitriptan for short-term menstrual associated migraine prevention)	Should be considered	Amitriptyline	Strong recommendation (moderate quality of evidence)	Nadolol, gabapentin, candesartan, butterbur
Possibly effective	Angiotensin converting enzyme (ACE) inhibitors (lisinopril), angiotensive receptor blockers (candesartan), alpha-agonists (clonidine, guanfacine), AEDs (carbamazepine), beta-blockers (nebivolol, pindolol)	Can be considered	Candesartan, valproate	Strong recommendation (low quality of evidence)	Riboflavin, coenzymeQ, magnesium
Conflicting, inadequate	Anti-depressants (fluoxetine, fluvoxamine, protriptyline), anti-thrombotics (acenocoumarol, coumadin, picotamide), beta-blockers (bisoprolol), calcium channel blockers (nicardipine, nifedipine, nimodipine, verapamil), acetazolamide, cyclandelate			Weak recommendation (high quality of evidence)	Divalproex, flunarizine, pizotifen
Ineffective (should not be offered)	Lamotrigine			Weak recommendation (low quality of evidence)	Venlafaxine, verapamil, lisinopril
Probably ineffective	Clomipramine				
Possibly ineffective	Acebutolol, clonazepam, nabumetone, oxcarbazepine, telmisartan				

[a]Aside from Botox, all recommendations for episodic and chronic migraine.

Table A-3. Guidelines on Single Interventions

Guideline	Intervention	Comment
2016 National Institute for Health and Care Excellence	Supraorbital nerve stimulation	Current evidence on transcutaneous electrical stimulation of the supraorbital nerve for treating and preventing migraine raises no major safety concerns. The evidence on efficacy is limited in quantity and quality. Therefore, this procedure should be used only with special arrangements for clinical governance, consent, and audit or research.
2019 European Headache Federation	Calcitonin Gene-Related Peptide (CGRP) antagonists	"In patients with episodic migraine who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance, we suggest the use of erenumab, fremanezumab, or galcanezumab. In patients with chronic migraine who have failed at least two of the available medical treatments or who cannot use other preventive treatments because of comorbidities, side effects or poor compliance, we suggest the use of erenumab, fremanezumab, or galcanezumab."
2016 American Academy of Neurology	Botox	Botox should be offered as a treatment option to patients with chronic migraine to increase the number of headache-free days. Botox should not be offered as treatment for episodic migraine.

Appendix B. Search Strategy

Randomized Controlled Trials

Embase.com (searches Medline and EMBASE together; no date limits applied)—Last searched June 24, 2020 (see Tables B-1 and B-2).

Table B-1. Search strategy for Embase.com (Randomized Controlled Trials)

Set Number	Concept	Search Statement
1	Migraine	migrain*:ti OR migraine/de
2	Prevention/ prophylaxis	avoid*:ab,ti OR block*ab,ti OR guard*:ab,ti OR precaution*:ab,ti OR prevent*:ab,ti OR prevention/exp OR 'prevention and control'/exp OR prophyl*:ab,ti OR prophylaxis/exp OR protect*:ab,ti
3	Date limits/study designs/ publication types	[english]/lim NOT (abstract:nc OR annual:nc OR 'book'/exp OR 'case report'/exp OR conference:nc OR 'conference abstract':it OR 'conference paper'/exp OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR 'editorial'/exp OR editorial:it OR 'erratum'/exp OR letter:it OR 'note'/exp OR note:it OR meeting:nc OR sessions:nc OR 'short survey'/exp OR symposium:nc) AND ('randomized controlled trial'/exp OR random*:ti)
4	Combine concepts	1 AND 2 AND 3

PubMed (no date limits applied)—Last searched June 24, 2020

Table B-2. Search strategy for PubMed (Randomized Controlled Trials)

Set Number	Concept	Search Statement
1	Migraine	migrain*[ti] OR migraine disorders[mh]
2	Prevention/ prophylaxis	avoid*[tiab] OR block*[tiab] OR guard*[tiab] OR precaution*[tiab] OR prevent*[tiab] OR primary prevention[mh] OR prevention and control[sh] OR prophyl*[tiab] OR protect*[tiab] OR secondary prevention[mh]
3	Date limits/study designs/ publication types	1 AND 2 AND english[la]) NOT (case reports[pt] OR comment[pt] OR editorial[pt] OR letter[pt] OR news[pt]) AND (humans[mh] OR inprocess[sb] OR publisher[sb] OR pubmednotmedline[sb])
4	Combine concepts	3 AND (randomized controlled trial[pt] OR random*[ti])

Systematic Reviews, Meta-Analyses, and Cochrane reviews

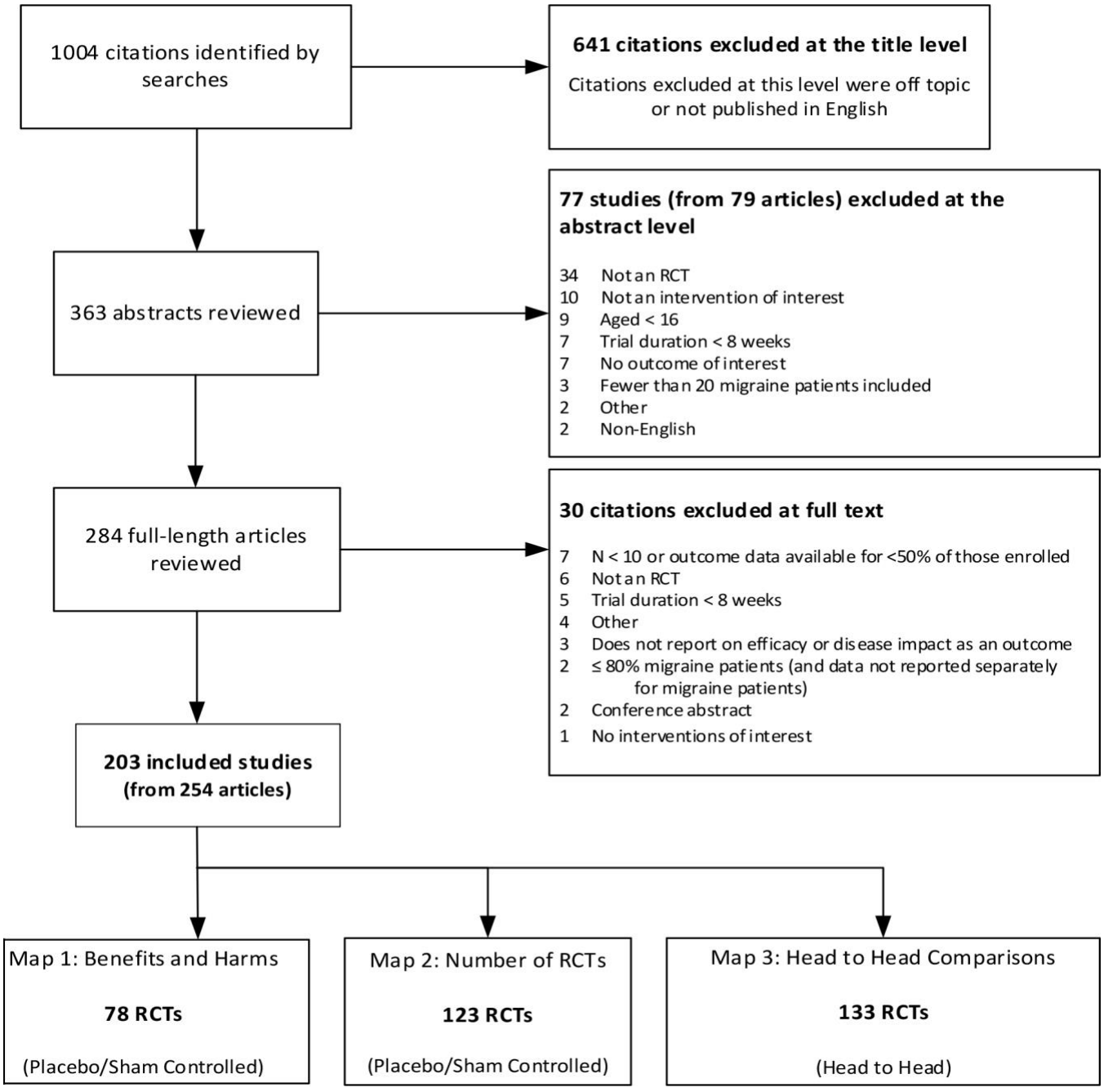
Embase.com (searches Medline and EMBASE together; 2000-2019)—Last searched December 16, 2019 (see Table B-3).

Table B-3. Search strategies for Embase.com (Systematic Reviews, Meta-analyses, and Cochrane Reviews)

Set Number	Concept	Search Statement
1	Migraine	migrain*:ti OR migraine/de
2	Prevention/ prophylaxis	avoid*:ti OR block*:ti OR guard*:ti OR precaution* OR prevent*:ti OR prevention/exp OR 'prevention and control'/exp OR prophyl*:ti OR prophylaxis/exp OR protect*:ti
3	Date limits/study designs/ publication types	([english]/lim AND [2000-2019]/py) NOT (abstract:nc OR annual:nc OR book/exp OR 'case report'/exp OR conference:nc OR 'conference abstract':it OR 'conference paper'/exp OR 'conference paper':it OR 'conference proceeding':pt OR 'conference review':it OR congress:nc OR editorial/exp OR editorial:it OR erratum/exp OR letter:it OR note/exp OR note:it OR meeting:nc OR sessions:nc OR 'short survey'/exp OR symposium:nc)
4	Study designs/ publication types	[cochrane review]/lim OR 'meta analysis'/exp OR metaanaly*:ti OR (meta* NEXT/1 analy*):ti OR random*:ti OR 'randomized controlled trial'/exp OR systematic*:ti OR 'systematic review'/exp
5	Combine concepts	1 AND 2 AND 3 AND 4

Appendix C. Flow Diagram

Figure C-1. Study Flow



RCT: Randomized controlled trial

Appendix D. Characteristics of Included Studies

We characterized type of migraine based on review of full-text articles as follows:

- **Episodic**: <15 migraines or headaches per month, or provided a mean with standard deviations (SDs) where the mean + 2 SDs < 15
- **Chronic**: ≥15 migraines or headaches per month
- **Episodic + chronic**: Studies that reported baseline only as a range of headaches that crossed >15 headaches per month
- **Not reported**: Studies that reported only migraines >2 per month and no other data OR studies that provided no description of baseline migraines/headaches per month
- **Other**: Studies that did not meet any of these criteria

Table D-1. Characteristics of Included Studies for Map 1 (Benefits and Harms)

Study Details	Patients	Interventions
Amitriptyline		
Reference: Couch 2011[29] **Country:** US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 391 **Mean age (years):** 34.9 **Gender (% female):** 81 **History of migraine:** NR **Type of migraine:** Episodic + chronic	Amitriptyline-—25 mg daily
Reference: Goncalves et al 2016[30] **Country:** Brazil **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 196 **Mean age (years):** 37 **Gender (% female):** 75 **History of migraine:** 22 years **Type of migraine:** Episodic	Amitriptyline—25 mg daily Melatonin—3 mg Placebo

Study Details	Patients	Interventions
Atogepant		
Reference: Goadsby et al 2020[31] **Country:** US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 834 **Mean age (years):** 40 **Gender (% female):** 87 **History of migraine:** 19 years **Type of migraine:** Episodic	Atogepant—10 mg once daily Atogepant—30 mg once daily Atogepant—60 mg once daily Atogepant—30 mg twice daily Atogepant—60 mg twice daily Placebo
Candesartan		
Reference: Stovner et al 2014[32] **Country:** Norway **Study design:** Crossover **Overall RoB:** High	**Number of randomized patients:** 72 **Mean age (years):** 37 **Gender (% female):** 87 **History of migraine:** 19 years **Type of migraine:** Episodic + chronic	Candesartan—16 mg Placebo Propranolol—160 mg slow-release
Reference: Trovnik et al 2003[33] **Country:** Norway **Study design:** Crossover **Overall RoB:** Unclear	**Number of randomized patients:** 60 **Mean age (years):** NR **Gender (% female):** NR **History of migraine:** NR **Type of migraine:** Episodic + chronic	Candesartan—16 mg Placebo
Eptinezumab		
Reference: Ashina et al 2020[34] **Country:** Georgia, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 898 **Mean age (years):** 39.8 **Gender (% female):** 84.3 **History of migraine:** 17.4 years **Type of migraine:** Episodic	Eptinezumab—30 mg/day, up to 4 doses Eptinezumab—100 mg/day, up to 4 doses Eptinezumab—300 mg/day, up to 4 doses Placebo
Reference: Dodick et al 2019[35] **Country:** Australia, Georgia, New Zealand, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 665 **Mean age (years):** 37 **Gender (% female):** 87 **History of migraine:** 17.9 **Type of migraine:** Chronic + medication overuse	Eptinezumab—10 mg, single dose Eptinezumab—30 mg, single dose Eptinezumab—100 mg, single dose Eptinezumab—300 mg, single dose Placebo

Study Details	Patients	Interventions
Eptinezumab		
Reference: Lipton et al 2020[36] **Country:** Belgium, Czech Republic, Denmark, Georgia, Germany, Hungary, Italy, Russia, Slovakia, Spain, Ukraine, UK, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 1121 **Mean age (years):** 40.5 **Gender (% female):** 88.2 **History of migraine:** 18.1 years **Type of migraine:** Chronic	Eptinezumab—100 mg, up to 2 doses Eptinezumab—300 mg, up to 2 doses Placebo
Erenumab		
Reference: Dodick et al 2018[37] **Country:** Denmark, France, Greece, Portugal, Russia, Spain, Switzerland, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 577 **Mean age (years):** 42 **Gender (% female):** 85 **History of migraine:** 21 years **Type of migraine:** Episodic	Erenumab—70-mg monthly injection Placebo
Reference: Goadsby et al 2017[38] **Country:** Austria, Belgium, Canada, Czech Republic, Finland, Germany, Netherlands, Poland, Slovakia, Sweden, Turkey, UK, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 955 **Mean age (years):** 41 **Gender (% female):** 85 **History of migraine:** NR **Type of migraine:** Episodic	Erenumab—70 mg, subcutaneous Erenumab—140 mg, subcutaneous Placebo
Reference: Reuter et al 2018[39] **Country:** Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, Switzerland, UK **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 246 **Mean age (years):** 44 **Gender (% female):** 81 **History of migraine:** NR **Type of migraine:** Episodic	Erenumab—140 mg every 4 weeks Placebo

Study Details	Patients	Interventions
Erenumab		
Reference: Sakai et al 2019[40] **Country:** Japan **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 475 **Mean age (years):** 44.4 **Gender (% female):** 84.4 **History of migraine:** NR **Type of migraine:** Episodic	Erenumab—28 mg Erenumab—70 mg Erenumab—140 mg Placebo
Reference: Sun et al 2016[41] **Country:** Canada, Denmark, Finland, Germany, Norway, Portugal, Sweden, US **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 483 **Mean age (years):** 41.1 **Gender (% female):** 81 **History of migraine:** 21.3 years **Type of migraine:** Episodic	Erenumab—7 mg/month Erenumab—21 mg/month Erenumab—70 mg/month Placebo
Reference: Teppers et al 2017[42] **Country:** Canada, Czech Republic, Denmark, Finland, Germany, Norway, Poland, Sweden, UK, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 667 **Mean age (years):** 42 **Gender (% female):** 82.8 **History of migraine:** 21 years **Type of migraine:** Chronic	Erenumab—70 mg Erenumab—140 mg Placebo
Fremanezumab		
Reference: Bigal et al 2015a[43] **Country:** US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 297 **Mean age (years):** 41 **Gender (% female):** 88 **History of migraine:** 19 years **Type of migraine:** Episodic	Fremanezumab—225 mg one injection Fremanezumab—675 mg total over 3 injections Placebo
Reference: Bigal et al 2015b[44] **Country:** US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 264 **Mean age (years):** 40.7 **Gender (% female):** 86 **History of migraine:** 18.3 years **Type of migraine:** Chronic	Fremanezumab—900 mg/month Fremanezumab—225 to 675 mg/month Placebo

Study Details	Patients	Interventions
Fremanezumab		
Reference: Dodick et al 2018[45] **Country:** Canada, Czech Republic, Finland, Israel, Japan, Poland, Russia, Spain, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 875 **Mean age (years):** 41.8 **Gender (% female):** 85 **History of migraine:** 20 years **Type of migraine:** Episodic	Fremanezumab—monthly Fremanezumab—single higher dose Placebo
Reference: Ferrari et al 2019[46] **Country:** Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, Netherlands, Poland, Spain, Sweden, Switzerland, UK, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 838 **Mean age (years):** 46.2 **Gender (% female):** 83.6 **History of migraine:** 24.2 years **Type of migraine:** Episodic + chronic	Fremanezumab—675 mg, administered quarterly Fremanezumab—225 to 675 mg, administered monthly Placebo
Reference: Silberstein et al 2017[47] **Country:** US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 1130 **Mean age (years):** 41 **Gender (% female):** 88 **History of migraine:** 20 years **Type of migraine:** Chronic	Fremanezumab—675 mg, single injection at baseline Fremanezumab—3 injections, 1 per month, at doses of 675 mg, 225 mg, and 225 mg Placebo
Galcanezumab		
Reference: Detke et al 2018[48] **Country:** Argentina, Canada, Czech Republic, Germany, Israel, Italy, Mexico, Netherlands, Spain, Taiwan, UK, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 1117 **Mean age (years):** 41 **Gender (% female):** 85 **History of migraine:** 21 years **Type of migraine:** Chronic	Galcanezumab—120-mg injection once a month Galcanezumab—240-mg injection once a month Placebo
Reference: Dodick et al 2014b[49] **Country:** US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 218 **Mean age (years):** 41.3 **Gender (% female):** 85 **History of migraine:** NR **Type of migraine:** Episodic	Galcanezumab—150 mg, subcutaneous every 2 weeks Placebo

Study Details	Patients	Interventions
Galcanezumab		
Reference: Mulleners et al 2020[50] **Country:** Belgium, Canada, Czech Republic, France, Germany, Hungary, Japan, Netherlands, South Korea, Spain, UK, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 463 **Mean age (years):** 46 **Gender (% female):** 86 **History of migraine:** 23 years **Type of migraine**: Episodic + chronic	Galcanezumab—120-mg injection once a month Placebo
Reference: Sakai et al 2020[51] **Country:** Japan **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 459 **Mean age (years):** 44 **Gender (% female):** 84 **History of migraine:** 21 years **Type of migraine:** Episodic	Galcanezumab—120 mg per month (1 injection a month) Galcanezumab—240 mg per month (1 injection a month) Placebo
Reference: Skljarevski et al 2018a[52] **Country:** US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 410 **Mean age (years):** 40.2 **Gender (% female):** 83 **History of migraine:** NR **Type of migraine:** Episodic	Galcanezumab—5 mg Galcanezumab—50 mg Galcanezumab—120 mg Galcanezumab—300 mg Placebo
Reference: Skljarevski et al 2018b[53] **Country:** Argentina, Czech Republic, Germany, Israel, Mexico, Netherlands, South Korea, Spain, Taiwan, UK, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 922 **Mean age (years):** 42 **Gender (% female):** 85 **History of migraine:** 20 years **Type of migraine:** Episodic	Galcanezumab—120 mg/month Galcanezumab—240 mg/month Placebo
Reference: Stauffer et al 2018[54] **Country:** US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 862 **Mean age (years):** 40.7 **Gender (% female):** 84 **History of migraine:** 20.1 years **Type of migraine:** Episodic	Galcanezumab—120 mg per month Galcanezumab—240 mg per month Placebo

Study Details	Patients	Interventions
Lisinopril		
Reference: Schrader et al 2001[55] **Country:** Norway **Study design:** Crossover **Overall RoB:** High	**Number of randomized patients:** 60 **Mean age (years):** 41 **Gender (% female):** 81 **History of migraine:** NR **Type of migraine:** Episodic	Lisinopril—10 mg/day Placebo
Metoprolol		
Reference: Andersson et al 1983[56] **Country:** Denmark, Sweden **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 71 **Mean age (years):** NR **Gender (% female):** 84.5 **History of migraine:** NR **Type of migraine:** Episodic	Metoprolol—200 mg Placebo
Reference: Bayer et al 2019[57] **Country:** Germany **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 130 **Mean age (years):** 43.6 **Gender (% female):** 60.8 **History of migraine:** NR **Type of migraine:** NR	Metoprolol—47.5 to 95 mg/day Placebo
Reference: Steiner et al 1988[58] **Country:** UK **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 59 **Mean age (years):** 37 **Gender (% female):** 23.8 **History of migraine:** NR **Type of migraine:** Episodic	Metoprolol—50 mg, twice daily Placebo
Noninvasive Vagal Nerve Stimulation		
Reference: Diener et al 2019[59] **Country:** Belgium, Denmark, Germany, Greece, Netherlands, Norway, Spain, UK **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 341 **Mean age (years):** 42 **Gender (% female):** 84 **History of migraine:** NR **Type of migraine:** Episodic	Noninvasive vagal nerve stimulation (gammaCore) Sham

Study Details	Patients	Interventions
OnabotulinumtoxinA		
Reference: Anand et al 2006[60] **Country:** India **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 32 **Mean age (years):** NR **Gender (% female):** 75 **History of migraine:** NR **Type of migraine:** Episodic	OnabotulinumtoxinA—50 U Placebo
Reference: Aurora et al 2007[61] **Country:** Canada, US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 369 **Mean age (years):** 45 **Gender (% female):** 89.2 **History of migraine:** 22.7 years **Type of migraine:** Episodic	OnabotulinumtoxinA—100 Units Placebo
Reference: Aurora et al 2010[62] **Country:** Canada, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 679 **Mean age (years):** 42 **Gender (% female):** 87 **History of migraine:** NR **Type of migraine:** Chronic	OnabotulinumtoxinA—155 to 195 U injected twice Placebo
Reference: Barrientos and Chana 2003[63] **Country:** Chile **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 30 **Mean age (years):** 41.1 **Gender (% female):** 80 **History of migraine:** 15.6 years **Type of migraine:** Episodic	OnabotulinumtoxinA—50 U Placebo
Reference: Cady and Schreiber 2008[64] **Country:** US **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 61 **Mean age (years):** 42 **Gender (% female):** 85 **History of migraine:** NR **Type of migraine:** Episodic + chronic	OnabotulinumtoxinA—139 U, one set of injections Placebo
Reference: Diener et al 2010[65] **Country:** Germany, Sweden, US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 705 **Mean age (years):** 41 **Gender (% female):** 85.4 **History of migraine:** 18 years **Type of migraine:** Chronic	OnabotulinumtoxinA—155 Units Placebo

Study Details	Patients	Interventions
OnabotulinumtoxinA		
Reference: Elkind et al 2006[6] **Country:** US **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 418 **Mean age (years):** 44 **Gender (% female):** 85 **History of migraine:** 21 years **Type of migraine:** Episodic	OnabotulinumtoxinA—7.5 U, single set of injections OnabotulinumtoxinA—25 U OnabotulinumtoxinA—50 U Placebo
Reference: Evers et al 2004[66] **Country:** Germany **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 60 **Mean age (years):** 38 **Gender (% female):** 83 **History of migraine:** 22 years **Type of migraine:** Episodic + tension type	OnabotulinumtoxinA—100 units (frontal + neck) OnabotulinumtoxinA—16 units (frontal), placebo for neck Placebo
Reference: Freitag et al 2008[67] **Country:** US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 60 **Mean age (years):** 42 **Gender (% female):** 73 **History of migraine:** NR **Type of migraine:** Chronic	OnabotulinumtoxinA—100 U, one set of injections Placebo
Reference: Hou et al 2015[68] **Country:** China **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 102 **Mean age (years):** 41 **Gender (% female):** 75 **History of migraine:** 6 years **Type of migraine:** Episodic + chronic	OnabotulinumtoxinA—fixed sites 25 U OnabotulinumtoxinA—Acupoints 25 U Placebo
Reference: Pijpers et al 2019[69] **Country:** Netherlands **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 179 **Mean age (years):** 45.2 **Gender (% female):** 76 **History of migraine:** 27 years **Type of migraine:** Chronic + medication overuse	OnabotulinumtoxinA—155 units Placebo
Reference: Relja et al 2007[5] **Country:** Belgium, Croatia, Denmark, Finland, France, Germany, Norway, Switzerland, UK **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 495 **Mean age (years):** 43 **Gender (% female):** 88 **History of migraine:** 23 years **Type of migraine:** Episodic	OnabotulinumtoxinA—225 U, single set of injections OnabotulinumtoxinA—150 U, single set of injections OnabotulinumtoxinA—75 U Placebo

Study Details	Patients	Interventions
OnabotulinumtoxinA		
Reference: Sandrini et al 2011[70] **Country:** Italy **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 68 **Mean age (years):** 48.8 **Gender (% female):** 80.4 **History of migraine:** 20 years **Type of migraine:** Chronic + medication overuse	OnabotulinumtoxinA—100 U Placebo
Reference: Saper et al 2007[71] **Country:** US **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 232 **Mean age (years):** 43.6 **Gender (% female):** 85.8 **History of migraine:** 23.8 years **Type of migraine:** Episodic	OnabotulinumtoxinA—10 U, frontal administration OnabotulinumtoxinA—6 U, temporal administration OnabotulinumtoxinA—9 U, glabellar administration OnabotulinumtoxinA—25 U, frontal, temporal, and glabellar administration Placebo
Reference: Silberstein et al 2000[72] **Country:** US **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 123 **Mean age (years):** 44 **Gender (% female):** 85 **History of migraine:** 23 years **Type of migraine:** Episodic	OnabotulinumtoxinA—25 U, single set of injections OnabotulinumtoxinA—75 U, single set of injections Placebo
Reference: Silberstein et al 2005[21] **Country:** Canada, US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 702 **Mean age (years):** 43.4 **Gender (% female):** 82.9 **History of migraine:** 13.7 years **Type of migraine:** Chronic	OnabotulinumtoxinA—225 U OnabotulinumtoxinA—150 U OnabotulinumtoxinA—75 U Placebo
Reference: Vo et al 2007[73] **Country:** US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 49 **Mean age (years):** 43 **Gender (% female):** 85 **History of migraine:** 20 years **Type of migraine:** Episodic + chronic	OnabotulinumtoxinA—135 to 205 U, single set of injections Placebo—single set of injections

Study Details	Patients	Interventions
Propranolol		
Reference: al-Qassab and Findley 1993[74] **Country:** UK **Study design:** Crossover **Overall RoB:** High	**Number of randomized patients:** 45 **Mean age (years):** 36 **Gender (% female):** 80 **History of migraine:** 9 years **Type of migraine:** Episodic + chronic	Propranolol—160 mg/day (long-acting) Propranolol—80 mg/day (long-acting) Placebo
Reference: Dahlof 1987[75] **Country:** Sweden **Study design:** Crossover **Overall RoB:** Unclear	**Number of randomized patients:** 28 **Mean age (years):** NR **Gender (% female):** NR **History of migraine:** NR **Type of migraine:** Episodic	Propranolol—40 mg 3 times a day Placebo
Reference: Diener et al 1996[76] **Country:** NR **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 214 **Mean age (years):** 39 **Gender (% female):** 78 **History of migraine:** 19 years **Type of migraine:** Episodic	Propranolol—120 mg/day Cyclandelate—dose range not reported Placebo
Reference: Diener et al 2004[77] **Country:** Australia, Denmark, Finland, Germany, Italy, Netherlands, South Africa, South Korea, Spain, Sweden, Taiwan, UK **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 575 **Mean age (years):** 40.9 **Gender (% female):** 79.8 **History of migraine:** NR **Type of migraine:** Episodic	Propranolol—160 mg/day Topiramate—100 mg/day Topiramate—200 mg/day Placebo
Reference: Forssman et al 1976[78] **Country:** Sweden **Study design:** Crossover **Overall RoB:** Unclear	**Number of randomized patients:** 32 **Mean age (years):** 37.4 **Gender (% female):** 87.5 **History of migraine:** 18.9 years **Type of migraine:** Episodic	Propranolol—40 mg Placebo
Reference: Pradalier et al 1989[79] **Country:** France **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 74 **Mean age (years):** 37.4 **Gender (% female):** 75.7 **History of migraine:** NR **Type of migraine:** Episodic	Propranolol—160 mg/day Placebo

Study Details	Patients	Interventions
Propranolol		
Reference: Sargent et al 1985[80] **Country:** US **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 161 **Mean age (years):** 30 **Gender (% female):** 79 **History of migraine:** 20 years **Type of migraine:** Episodic	Propranolol—40 mg 3 times a day Naproxen—550 mg twice daily Placebo
Reference: Stovner et al 2014[32] **Country:** Norway **Study design:** Crossover **Overall RoB:** High	**Number of randomized patients:** 72 **Mean age (years):** 37 **Gender (% female):** 82 **History of migraine:** 19 years **Type of migraine:** Episodic + chronic	Propranolol—160 mg slow-release Candesartan—16 mg Placebo
Reference: Tfelt et al 1984[81] **Country:** Denmark, Finland, Norway **Study design:** Crossover **Overall RoB:** Unclear	**Number of randomized patients:** 96 **Mean age (years):** 39.5 **Gender (% female):** 74 **History of migraine:** 20.9 years **Type of migraine:** Episodic	Propranolol—80 mg twice daily Timolol—10 mg twice daily Placebo
Reference: Wideroe and Vigander 1974[82] **Country:** Norway **Study design:** Crossover **Overall RoB:**	**Number of randomized patients:** 30 **Mean age (years):** 38 **Gender (% female):** 86.7 **History of migraine:** NR **Type of migraine:** Episodic	Propranolol—160 mg/day Placebo
Topiramate		
Reference: Brandes et al 2004[83] **Country:** Canada, US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 483 **Mean age (years):** 39 **Gender (% female):** 87 **History of migraine:** NR **Type of migraine:** Episodic	Topiramate—50 mg daily Topiramate—100 mg daily Topiramate—200 mg daily Placebo
Reference: de Tommaso et al 2007[84] **Country:** Italy **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 45 **Mean age (years):** 37.9 **Gender (% female):** 77.8 **History of migraine:** NR **Type of migraine:** NR	Topiramate—100 mg daily Placebo Levitaracetam—1000 mg daily

Study Details	Patients	Interventions
Topiramate		
Reference: Diener et al 2004[77] **Country:** Australia, Denmark, Finland, Germany, Italy, Netherlands, South Africa, South Korea, Spain, Sweden, Taiwan, UK **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 575 **Mean age (years):** 40.9 **Gender (% female):** 79.8 **History of migraine:** NR **Type of migraine:** Episodic	Topiramate—100 mg/day Topiramate—200 mg/day Propranolol—160 mg/day Placebo
Reference: Diener et al 2007a[85] **Country:** Austria, Belgium, Bulgaria, Czech Republic, Denmark, France, Germany, Greece, Hungary, Ireland, Italy, Norway, Poland, Portugal, Russia, Saudi Arabia, Slovenia, Spain, Switzerland, Turkey, UK **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 514 **Mean age (years):** 39.8 **Gender (% female):** 87 **History of migraine:** NR **Type of migraine:** Episodic	Topiramate—50 to 200 mg daily Placebo
Reference: Diener et al 2007b[86] **Country:** NR **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 59 **Mean age (years):** 46 **Gender (% female):** 75 **History of migraine:** NR **Type of migraine:** Chronic	Topiramate—50 to 200 mg/day Placebo
Reference: Lipton et al 2011[87] **Country:** US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 385 **Mean age (years):** 40 **Gender (% female):** 89 **History of migraine:** 20 years **Type of migraine:** Episodic	Topiramate—100 mg daily Placebo
Reference: Mei et al 2004[88] **Country:** Italy **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 115 **Mean age (years):** 39 **Gender (% female):** 54 **History of migraine:** NR **Type of migraine:** Episodic	Topiramate—100 mg Placebo

Study Details	Patients	Interventions
Topiramate		
Reference: Mei et al 2006[89] **Country:** Italy **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 50 **Mean age (years):** 45.9 **Gender (% female):** 68.6 **History of migraine:** 5.0 years **Type of migraine:** Chronic + medication overuse	Topiramate—titrated from 25 to 100 mg/day Placebo
Reference: Silberstein et al 2004[90] **Country:** US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 487 **Mean age (years):** 40 **Gender (% female):** 89 **History of migraine:** NR **Type of migraine:** Episodic	Topiramate—50 mg/day Topiramate—100 mg/day Topiramate—200 mg/day Placebo
Reference: Silberstein et al 2006[91] **Country:** US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 213 **Mean age (years):** 40.5 **Gender (% female):** 85.8 **History of migraine:** NR **Type of migraine:** Episodic	Topiramate—200 mg daily Placebo
Reference: Silberstein et al 2007[92] **Country:** US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 328 **Mean age (years):** 38.2 **Gender (% female):** 85.3 **History of migraine:** 9.2 years **Type of migraine:** Chronic	Topiramate—100 mg/day Placebo
Reference: Silvestrini et al 2003[93] **Country:** Italy **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 28 **Mean age (years):** 43.5 **Gender (% female):** 64 **History of migraine:** NR **Type of migraine**: Chronic + medication overuse	Topiramate—50 mg daily Placebo
Reference: Storey et al 2001[94] **Country:** US **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 40 **Mean age (years):** 38.2 **Gender (% female):** 97.5 **History of migraine:** NR **Type of migraine:** Episodic	Topiramate—200 mg daily Placebo

Study Details	Patients	Interventions
Transcutaneous Supraorbital Nerve Stimulation		
Reference: Schoenen et al 2013[19] **Country:** Belgium **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 67 **Mean age (years):** 37 **Gender (% female):** 91 **History of migraine:** 16 years **Type of migraine:** Episodic	Transcutaneous supraorbital nerve stimulation—Cefaly Sham
Valproate/Valproic Acid		
Reference: Ebrahimi-Monfared et al 2017[12] **Country:** Iran **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 126 **Mean age (years):** 38.9 **Gender (% female):** 51 **History of migraine:** 7.4 years **Type of migraine:** Chronic	Valproate/valproic acid—200 mg daily Melatonin—3 mg Placebo
Reference: Freitag et al 2002[13] **Country:** US **Study design:** Parallel **Overall RoB:** Low	**Number of randomized patients:** 239 **Mean age (years):** 41 **Gender (% female):** 79 **History of migraine:** 20 years **Type of migraine:** Episodic	Valproate/valproic acid—500 to 1000 mg/day Placebo
Reference: Jensen et al 1994[14] **Country:** Denmark **Study design:** Crossover **Overall RoB:** High	**Number of randomized patients:** 43 **Mean age (years):** 46 **Gender (% female):** 86 **History of migraine:** NR **Type of migraine:** Episodic	Valproate/valproic acid—1000 to 1500 mg/day Placebo
Reference: Klapper 1997[15] **Country:** US **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 176 **Mean age (years):** 40.8 **Gender (% female):** 89 **History of migraine:** 21.6 years **Type of migraine:** Episodic	Valproate/valproic acid—500 mg/day Valproate/valproic acid—1000 mg/day Valproate/valproic acid—1500 mg/day Placebo
Reference: Mathew et al 1995[16] **Country:** US **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 107 **Mean age (years):** 45.6 **Gender (% female):** 78 **History of migraine:** NR **Type of migraine:** Episodic	Valproate/valproic acid—titrated between 250 and 750 mg/day Placebo

Study Details	Patients	Interventions
Valproate/Valproic Acid		
Reference: Sadeghian and Motiei-Langroudi 2015[17] **Country:** NR **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 105 **Mean age (years):** 35 **Gender (% female):** 73 **History of migraine:** 5 months **Type of migraine:** NR	Valproate/valproic acid—500 mg/day Levitaracetam—250 to 500 mg/day Placebo
Reference: Yurekli et al 2008[18] **Country:** Turkey **Study design:** Parallel **Overall RoB:** Unclear	**Number of randomized patients:** 29 **Mean age (years):** 40.1 **Gender (% female):** 87.5 **History of migraine:** NR **Type of migraine:** Chronic	Valproate/valproic acid—500 to 1000 mg/day Placebo
Venlafaxine		
Reference: Ozyalcin et al 2005[20] **Country:** Turkey **Study design:** Parallel **Overall RoB:** High	**Number of randomized patients:** 60 **Mean age (years):** 36.5 **Gender (% female):** 90 **History of migraine:** NR **Type of migraine:** Episodic	Venlafaxine—75 mg daily Venlafaxine—150 mg Placebo

Table D-2. Studies Included in Maps 2 or 3

Study	Included in Maps 2 or 3
Angiotensin Converting Enzyme (ACE) Inhibitor/Angiotensin Receptor Blocker (ARB)	
Diener et al 2009[95]	Map 2
Schrader et al 2001[55]	Map 2
Sonbolestan et al 2013[96]	Map 2
Stovner et al 2014[32]	Map 2, Map 3
Tronvik et al 2003[33]	Map 2
Alpha Agonist	
Adam et al 1978[97]	Map 2
Boisen et al 1978[98]	Map 2
Martucci et al 1985[99]	Map 2, Map 3
Mondrup and Moller 1977[100]	Map 2
Ryan et al 1975[101]	Map 2
Shafar et al 1972[102]	Map 2
Antiepileptic	
Afshari et al 2012[103]	Map 3
Ali et al 2010[104]	Map 3
Ashtari et al 2008[105]	Map 3
Bavrasad et al 2010[106]	Map 3
Blumenfeld et al 2008[107]	Map 3
Bostani et al 2013[108]	Map 3
Brandes et al 2004[83]	Map 2, Map 3
Cady et al 2011[109]	Map 3
Cady et al 2012[110]	Map 3
Chitsaz et al 2012a[111]	Map 3
Chitsaz et al 2012b[112]	Map 3
Choudhary et al 2017[113]	Map 3
Cosentino et al 2013[114]	Map 3

Study	Included in Maps 2 or 3
Antiepileptic	
Dakhale et al 2019[115]	Map 3
de Tommaso et al 2007[84]	Map 2, Map 3
Di et al 2000[116]	Map 2
Diener et al 2004[77]	Map 2, Map 3
Diener et al 2007a[85]	Map 2
Diener et al 2007b[86]	Map 2
Dodick et al 2009[117]	Map 3
Ebrahimi-Monfared et al 2017[12]	Map 2, Map 3
Facco et al 2013[118]	Map 3
Freitag et al 2002[13]	Map 2
Hering and Kuritzky 1992[119]	Map 2
Hesami et al 2018a[120]	Map 3
Hesami et al 2018b[121]	Map 3
Jensen et al 1994[14]	Map 2
Kalita et al 2013[122]	Map 3
Kaniecki 1997[123]	Map 3
Karimi et al 2019[124]	Map 3
Kashipazha et al 2017[125]	Map 3
Keskinbora and Aydinli 2008[126]	Map 3
Klapper 1997[15]	Map 2, Map 3
Krymchantowski et al 2012[127]	Map 3
Lai et al 2017[128]	Map 3
Lipton et al 2011[87]	Map 2
Liu et al 2017[129]	Map 3
Lo et al 2010[130]	Map 3
Luo et al 2012[131]	Map 3
Mansoureh et al 2008[132]	Map 3

Study	Included in Maps 2 or 3
Antiepileptic	
Mathew et al 1995[16]	Map 2
Mathew et al 2001[133]	Map 2
Mathew and Jaffri 2009[134]	Map 3
Mei et al 2004[88]	Map 2
Mei et al 2006[89]	Map 2
Millán-Guerrero et al 2008[135]	Map 3
Millán-Guerrero et al 2007[136]	Map 3
Mitsikostas and Polychronidis 1997[137]	Map 3
Mohammadianinejad et al 2011[138]	Map 3
Naderinabi et al 2017[139]	Map 3
Rahimdel et al 2015[140]	Map 3
Rodríguez-Leyva et al 2010[141]	Map 3
Sadeghian and Motiei-Langroudi 2015[17]	Map 2, Map 3
Shaygannejad et al 2006[142]	Map 3
Silberstein et al 2004[90]	Map 2, Map 3
Silberstein et al 2006[91]	Map 2
Silberstein et al 2007[92]	Map 2
Silberstein et al 2008[143]	Map 2
Silvestrini et al 2003[93]	Map 2
Spira and Beran 2003[144]	Map 2
Steiner et al 1997[145]	Map 2
Storey et al 2001[94]	Map 2
Varkey et al 2011[146]	Map 3
Xu and Mi 2017[147]	Map 3
Yang et al 2011[148]	Map 3
Yurekli et al 2008[18]	Map 2
Zain et al 2013[149]	Map 3

Study	Included in Maps 2 or 3
Beta-blocker	
Albers et al 1989[150]	Map 3
al-Qassab and Findley 1993[74]	Map 2, Map 3
Andersson et al 1983[56]	Map 2
Ashtari et al 2008[105]	Map 3
Bayer et al 2019[57]	Map 2
Bordini et al 1997[151]	Map 3
Borgesen 1976[152]	Map 2
Carroll et al 1990[153]	Map 3
Dahlof 1987[75]	Map 2, Map 3
Dakhale et al 2019[115]	Map 3
Diener et al 1996[76]	Map 2, Map 3
Diener et al 2001[154]	Map 3
Diener et al 2002[155]	Map 3
Diener et al 2004[77]	Map 2, Map 3
Domingues et al 2009[156]	Map 3
Forssman et al 1976[78]	Map 2
Forssman et al 1983[157]	Map 2, Map 3
Gawel et al 1992[158]	Map 3
Gerber et al 1995[159]	Map 3
Ghobadi and Jivad 2013[160]	Map 3
Hesse et al 1994[161]	Map 3
Johannsson et al 1987[162]	Map 2
Johnson et al 1986[163]	Map 2, Map 3
Kangasniemi et al 1984[164]	Map 3
Kaniecki 1997[123]	Map 3
Kaushik et al 2005[165]	Map 3
Kjaersgkd Rasmussen et al 1994[166]	Map 3

Study	Included in Maps 2 or 3
Beta-blocker	
Mathew 1981[167]	Map 2, Map 3
Mikkelsen et al 1986[168]	Map 2, Map 3
Millán-Guerrero et al 2014[169]	Map 3
Nadelmann et al 1986[170]	Map 2
Nambiar et al 2011[171]	Map 3
Pradalier et al 1989[79]	Map 2
Ryan 1984[172]	Map 3
Salviz et al 2016[173]	Map 3
Sargent et al 1985[80]	Map 2, Map 3
Schellenberg et al 2008[174]	Map 3
Shimell et al 1990[175]	Map 3
Sorensen et al 1991[176]	Map 3
Steiner et al 1988[58]	Map 2
Stellar et al 1984[177]	Map 2
Stovner et al 2014[32]	Map 2, Map 3
Streng et al 2006[178]	Map 3
Sudilovsky et al 1987[179]	Map 3
Tfelt-Hansen et al 1984[81]	Map 2, Map 3
Van De Ven et al 1997[180]	Map 2, Map 3
Weber and Reinmuth 1972[181]	Map 2
Wideroe and Vigander 1974[82]	Map 2
Ziegler et al 1987[182]	Map 2, Map 3
Ziegler et al 1993[183]	Map 2, Map 3
Botulinum Toxin Type A	
Anand et al 2006[60]	Map 2
Aurora et al 2007[61]	Map 2
Aurora et al 2010[62]	Map 2

Study	Included in Maps 2 or 3
Botulinum Toxin Type A	
Barrientos and Chana 2003[63]	Map 2
Blumenfeld et al 2008[107]	Map 3
Cady and Schreiber 2008[64]	Map 2
Cady et al 2011[109]	Map 3
Chankrachang et al 2011[184]	Map 2, Map 3
Chitsaz et al 2012a[111]	Map 3
Diener et al 2010[65]	Map 2
Elkind et al 2006[6]	Map 2, Map 3
Evers et al 2004[66]	Map 2, Map 3
Freitag et al 2008[67]	Map 2
Hou et al 2015[68]	Map 2, Map 3
Magalhaes et al 2010[185]	Map 3
Mathew and Jaffri 2009[134]	Map 3
Millán-Guerrero et al 2009[186]	Map 3
Naderinabi et al 2017[139]	Map 3
Petri et al 2009[187]	Map 2, Map 3
Pijpers et al 2019[69]	Map 2
Relja et al 2007[5]	Map 2, Map 3
Sandrini et al 2011[70]	Map 2
Saper et al 2007[71]	Map 2, Map 3
Shehata et al 2016[188]	Map 3
Silberstein et al 2000[72]	Map 2, Map 3
Silberstein et al 2005[21]	Map 2, Map 3
Vo et al 2007[73]	Map 2
Calcium Channel Blockers	
Ahuja and Verma 1985[189]	Map 2, Map 3
Albers et al 1989[150]	Map 3

Study	Included in Maps 2 or 3
Calcium Channel Blockers	
Ansell et al 1988[190]	Map 2
Gelmers et al 1989a[191]	Map 2
Gelmers et al 1989b[192]	Map 2
Ghobadi and Jivad 2013[160]	Map 3
Havanka-Kanniainen et al 1985[193]	Map 2, Map 3
Lamsudin and Sadjimin 1993[194]	Map 3
Leandri et al 1990[195]	Map 2
Markley et al 1984[196]	Map 2
McArthur et al 1989[197]	Map 2
Nuti et al 1996[198]	Map 3
Stewart et al 1988[199]	Map 2
Calcitonin Gene-Related Peptide (CGRP) Antagonist	
Ashina et al 2020[34]	Map 2, Map 3
Bigal et al 2015a[43]	Map 2, Map 3
Bigal et al 2015b[44]	Map 2, Map 3
Detke et al 2018[48]	Map 2, Map 3
Dodick et al 2014a[200]	Map 2
Dodick et al 2014b[49]	Map 2
Dodick et al 2018a[37]	Map 2
Dodick et al 2018b[45]	Map 2, Map 3
Dodick et al 2019[35]	Map 2, Map 3
Ferrari et al 2019[46]	Map 2, Map 3
Goadsby et al 2017[38]	Map 2, Map 3
Goadsby et al 2020[31]	Map 2, Map 3
Lipton et al 2020[36]	Map 2, Map 3
Mulleners et al 2020[50]	Map 2
Reuter et al 2018[39]	Map 2

Study	Included in Maps 2 or 3
Calcitonin Gene-Related Peptide (CGRP) Antagonist	
Sakai et al 2019[40]	Map 2, Map 3
Sakai et al 2020[51]	Map 2, Map 3
Silberstein et al 2017[47]	Map 2, Map 3
Skljarevski et al 2018a[52]	Map 2, Map 3
Skljarevski et al 2018b[53]	Map 2, Map 3
Stauffer et al 2018[54]	Map 2, Map 3
Sun et al 2016[41]	Map 2, Map 3
Tepper et al 2017[42]	Map 2, Map 3
Device	
Deng et al 2020[22]	Map 3
Diener et al 2019[59]	Map 2
Schoenen et al 2013[19]	Map 2
Other Antidepressant	
Adly et al 1992[201]	Map 2
Bank 1994[202]	Map 3
Bulut et al 2004[203]	Map 3
Colucci d'Amato et al 1999[204]	Map 2
Liu et al 2017[129]	Map 3
Ozyalcin et al 2005[20]	Map 2, Map 3
Rampello et al 2004[205]	Map 3
Salviz et al 2016[173]	Map 3
Saper et al 1994[206]	Map 2
Steiner et al 1998[207]	Map 2
Tarlaci 2009[208]	Map 3
Tricyclic Antidepressant	
Bank 1994[202]	Map 3
Bruno and Krymchantowski 2018[209]	Map 3

Study	Included in Maps 2 or 3
Tricyclic Antidepressant	
Bulut et al 2004[203]	Map 3
Couch and Hassanein 1979[210]	Map 2
Couch 2011[29]	Map 2
Dodick et al 2009[117]	Map 3
Domingues et al 2009[156]	Map 3
Gomersall and Stuart 1973[211]	Map 2
Goncalves et al 2016[30]	Map 2, Map 3
Kalita et al 2013[122]	Map 3
Keskinbora and Aydinli 2008[126]	Map 3
Krymchantowski et al 2002[212]	Map 3
Krymchantowski et al 2012[127]	Map 3
Lampl et al 2009[213]	Map 3
Magalhaes et al 2010[185]	Map 3
Mathew 1981[167]	Map 2, Map 3
Nelson et al 1998[214]	Map 3
Rampello et al 2004[205]	Map 3
Rodríguez-Leyva et al 2010[141]	Map 3
Santiago et al 2014[215]	Map 3
Villani et al 2017[216]	Map 3
Ziegler et al 1987[182]	Map 2, Map 3
Ziegler et al 1993[183]	Map 2, Map 3

Appendix E. Forest Plots

Forest plots below represent efficacy findings in terms of Hedges' *g* for each intervention. Within each plot, results are presented both by migraine type and overall (representing each migraine type filter option from the visualization). Each data point represents the longest follow-up timepoint reported in the study (consistent with the "Any" option for follow-up in the visualization). An asterisk (*) next to a study name indicates that the study reported results, but reporting was insufficient for inclusion in the meta-analysis.

Figure E-1. Amitriptyline

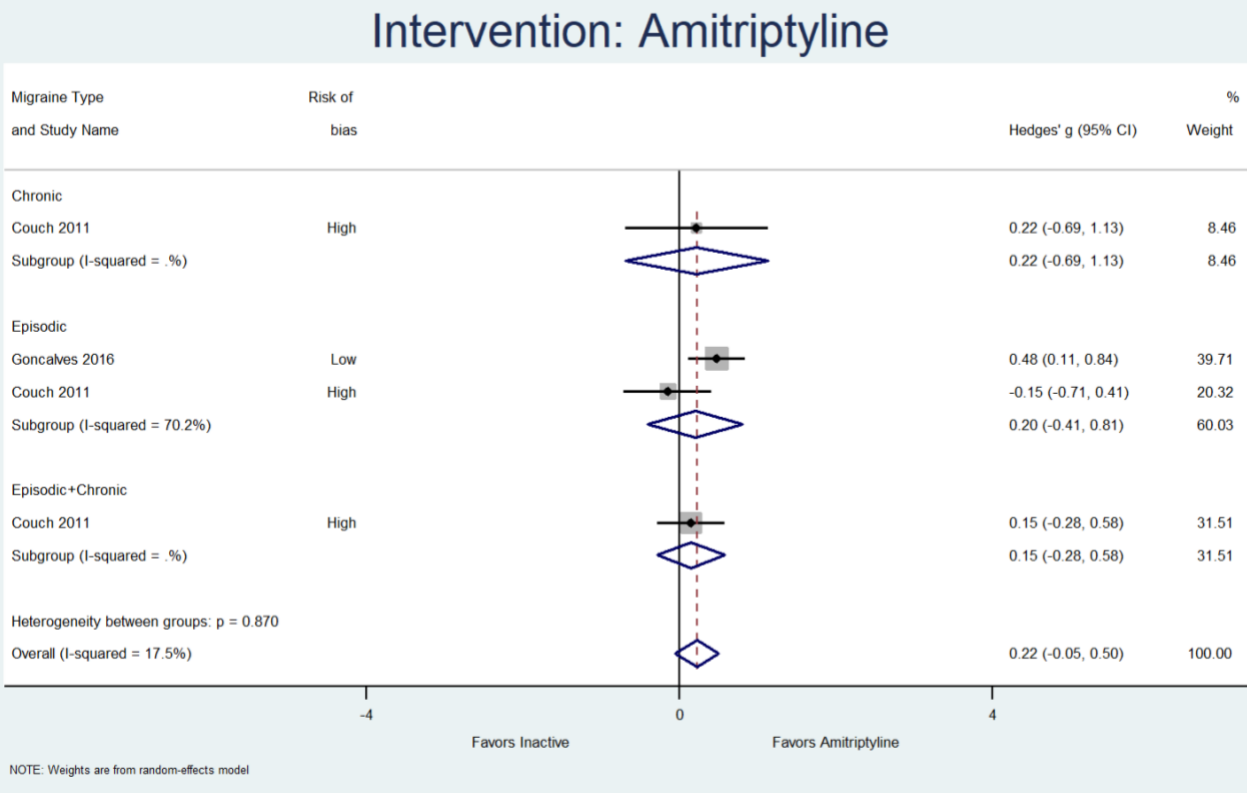


Figure E-2. Atogepant

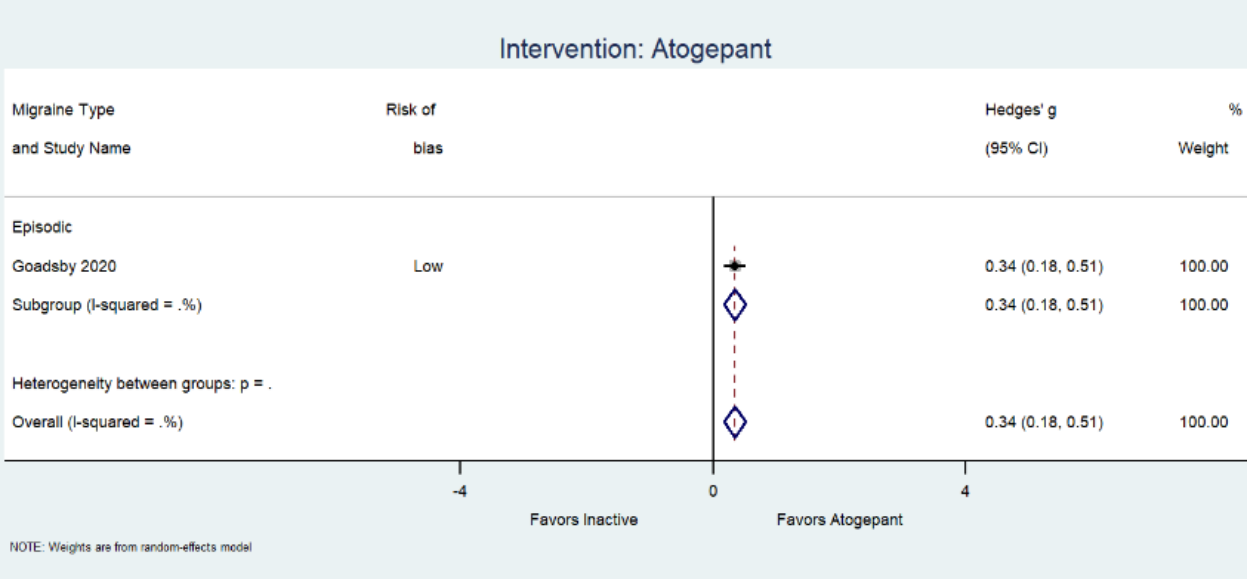


Figure E-3. Candesartan

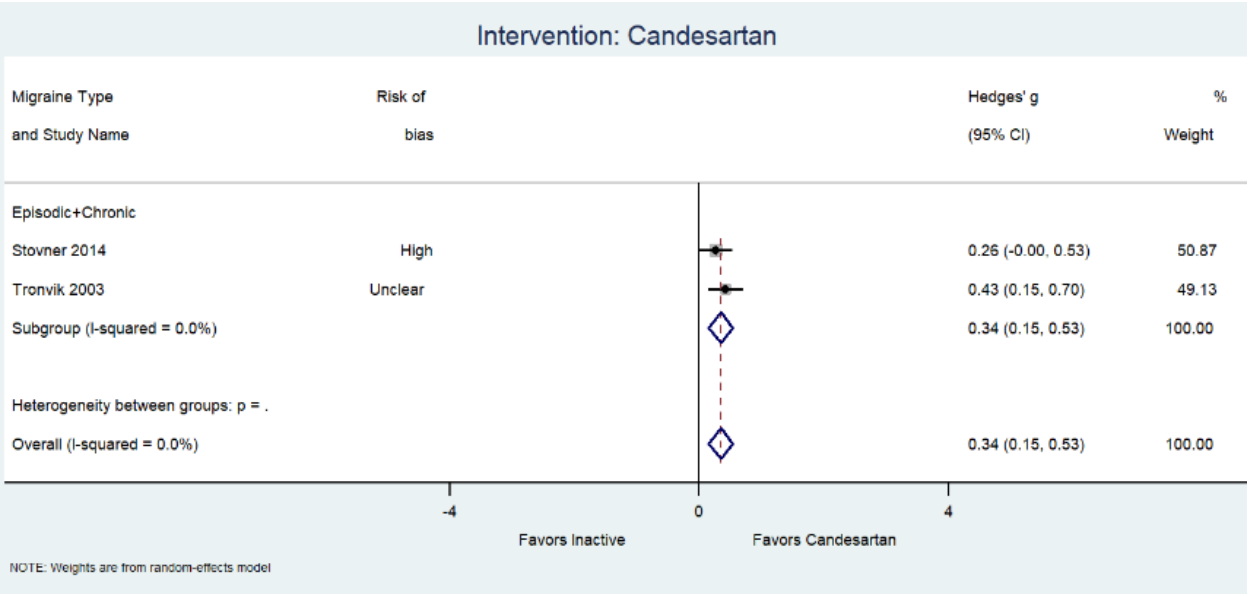


Figure E-4. Eptinezumab

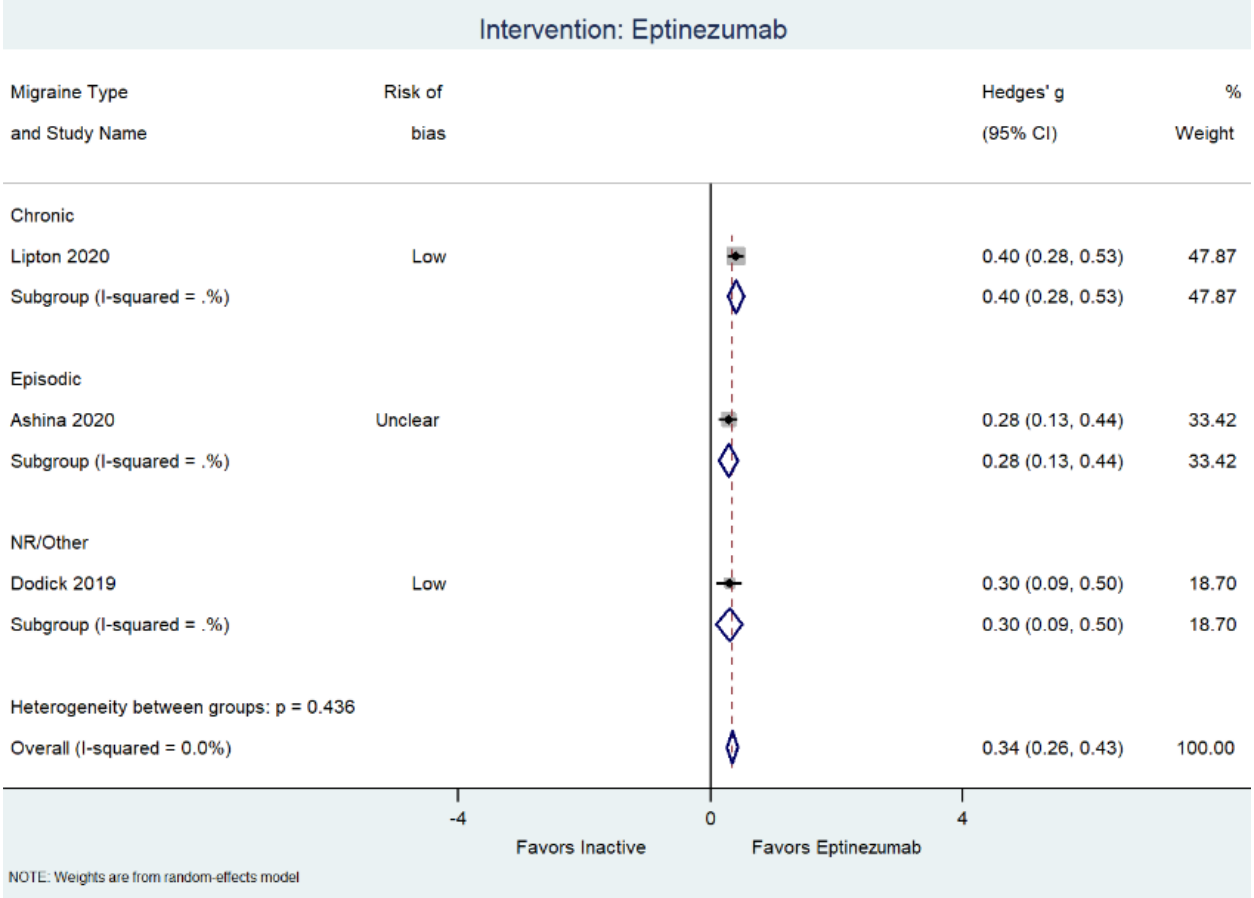


Figure E-5. Erenumab

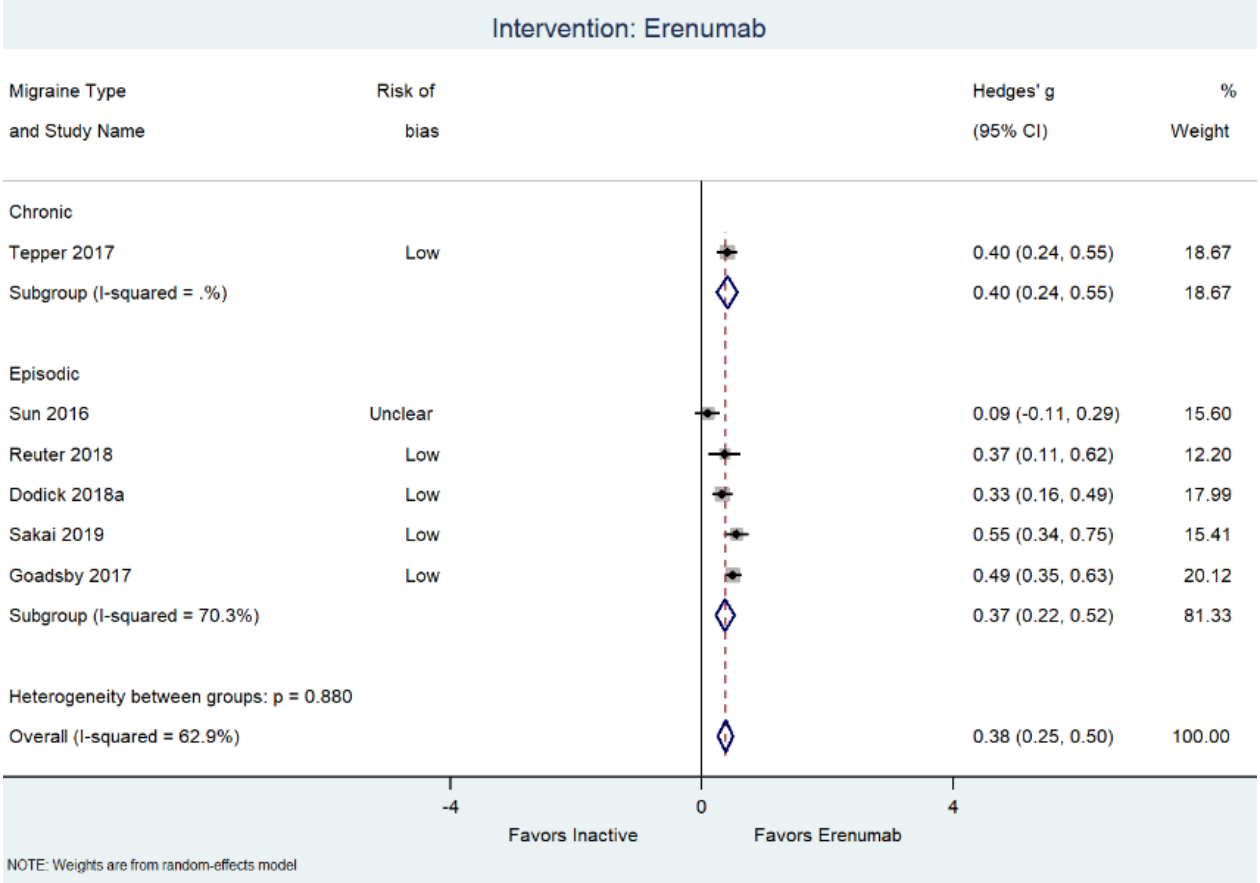


Figure E-6. Fremanezumab

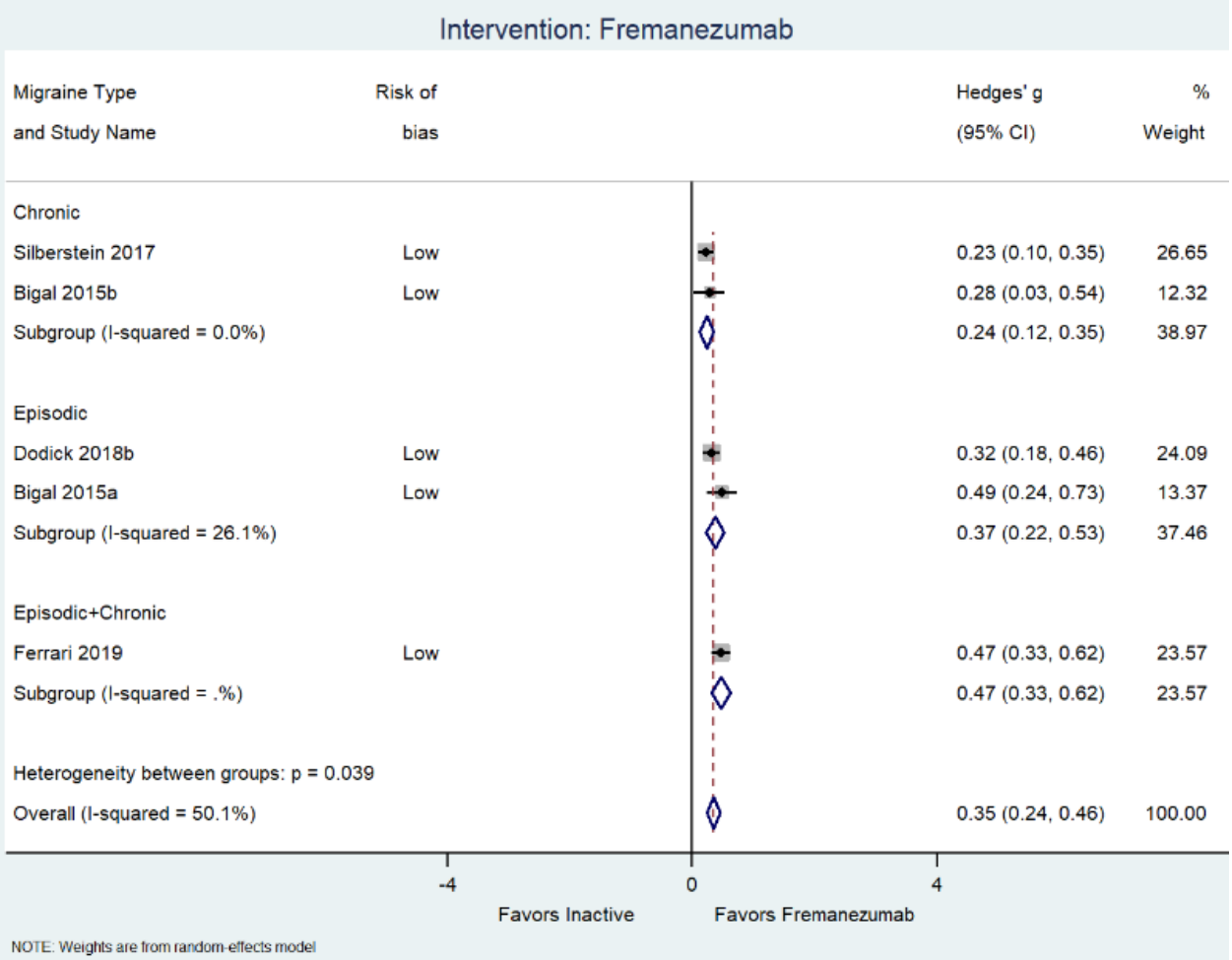


Figure E-7. Galcanezumab

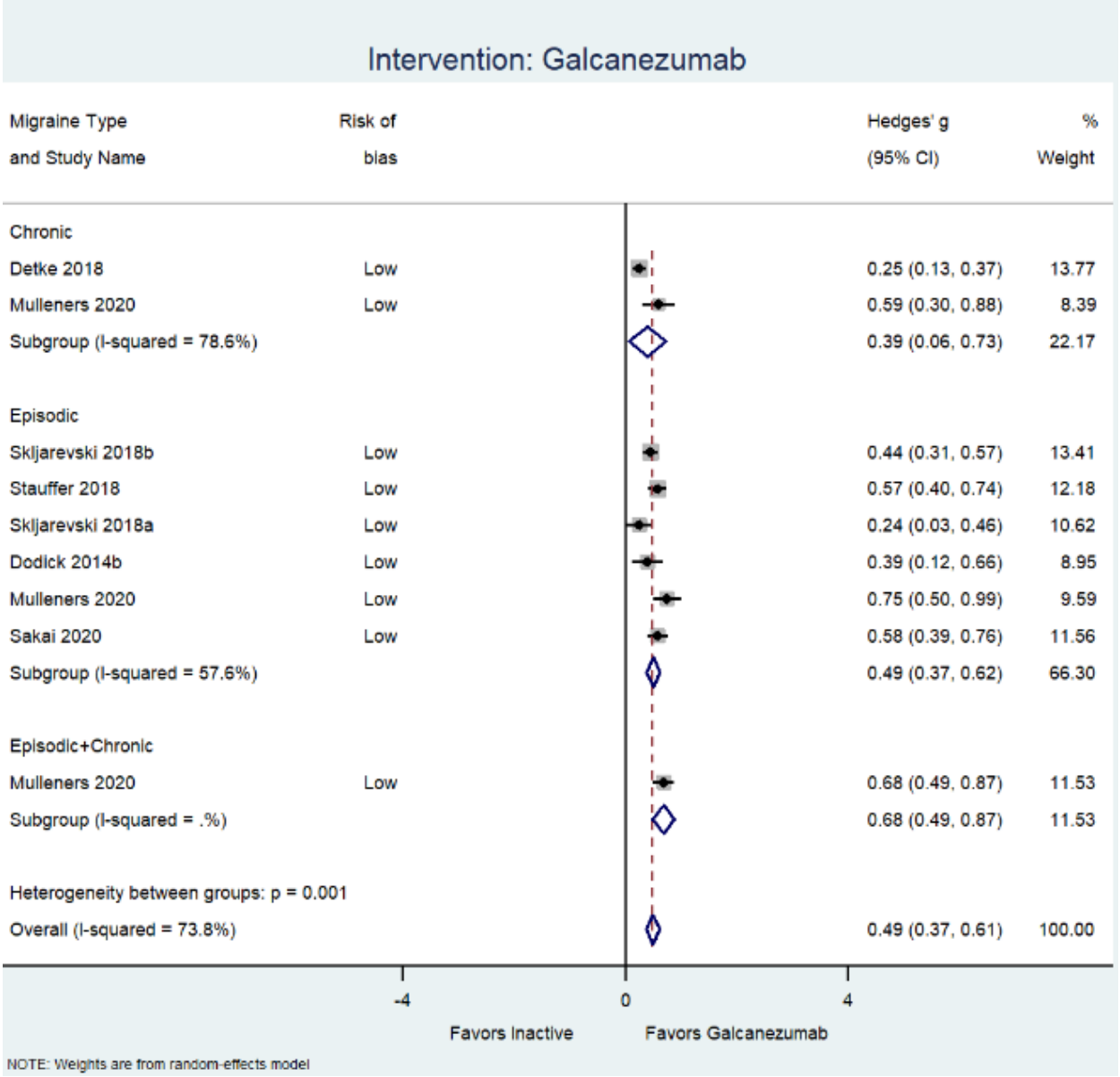


Figure E-8. Lisinopril

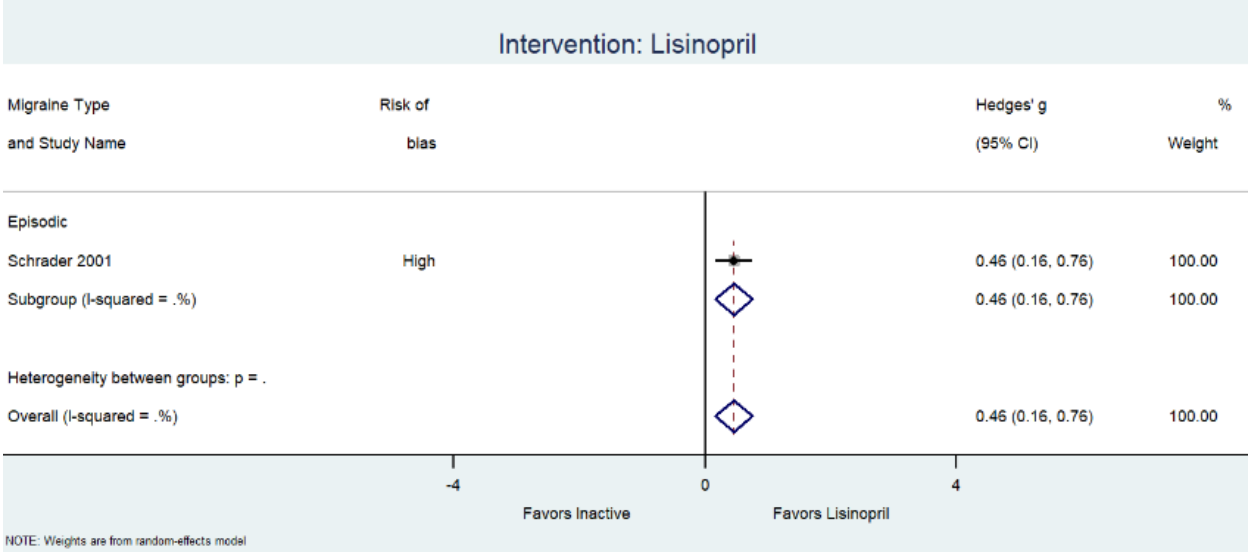


Figure E-9. Metoprolol

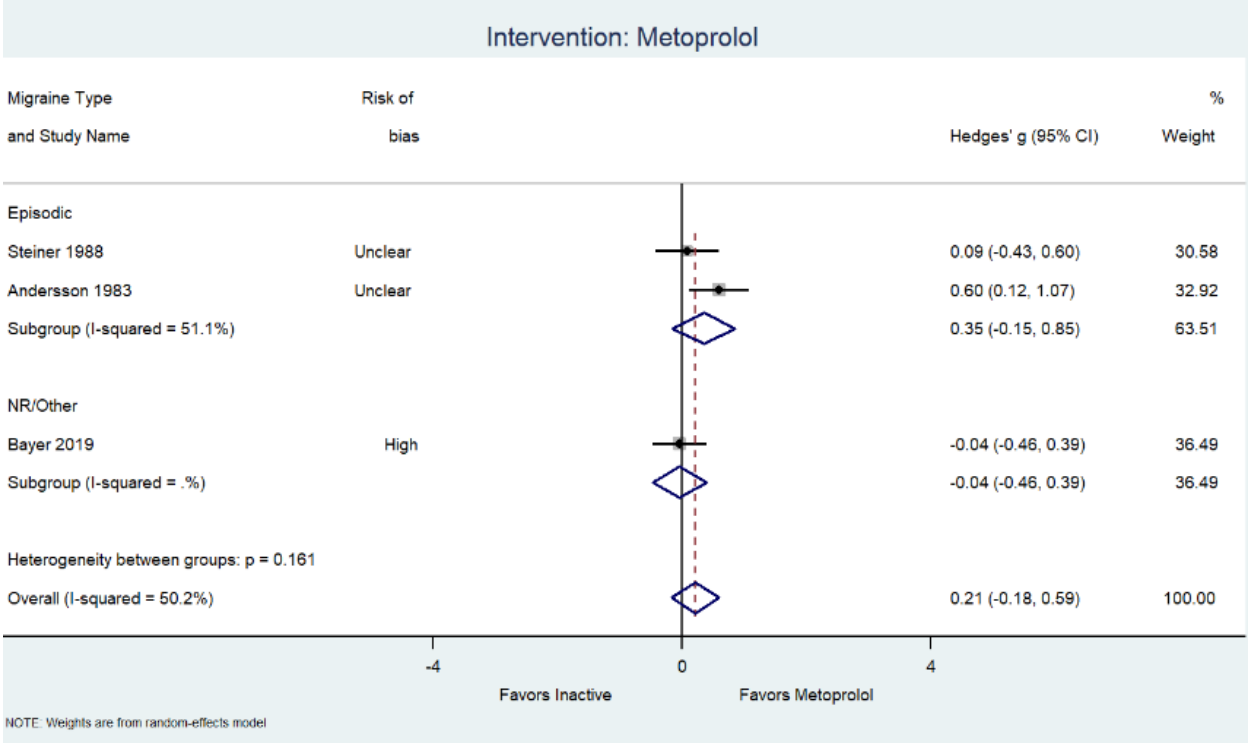


Figure E-10. Noninvasive Vagal Nerve Stimulation

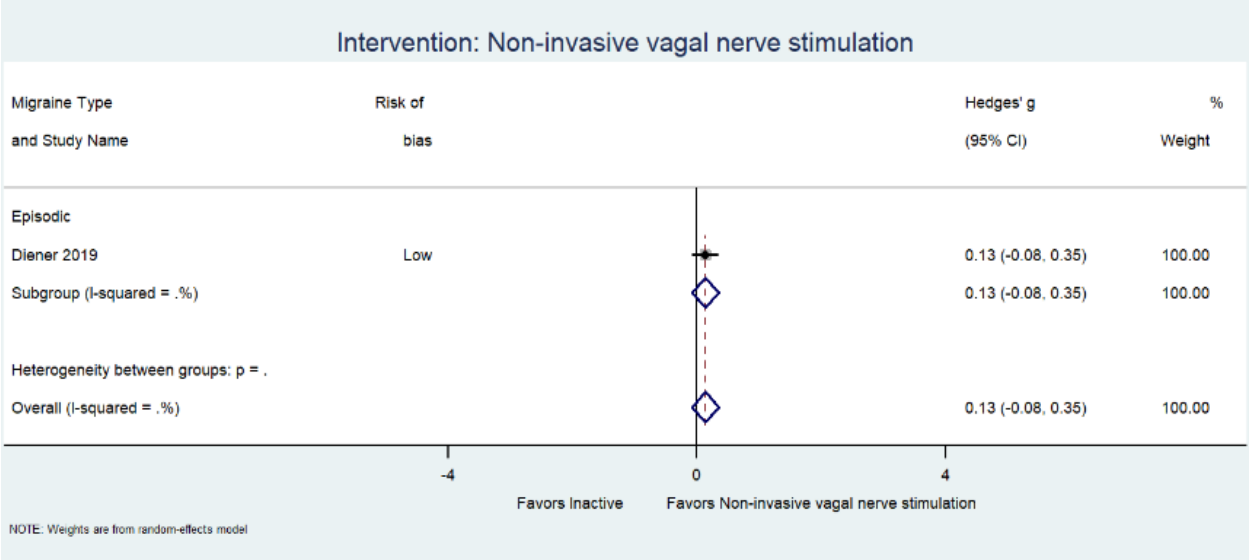


Figure E-11. OnabotulinumtoxinA

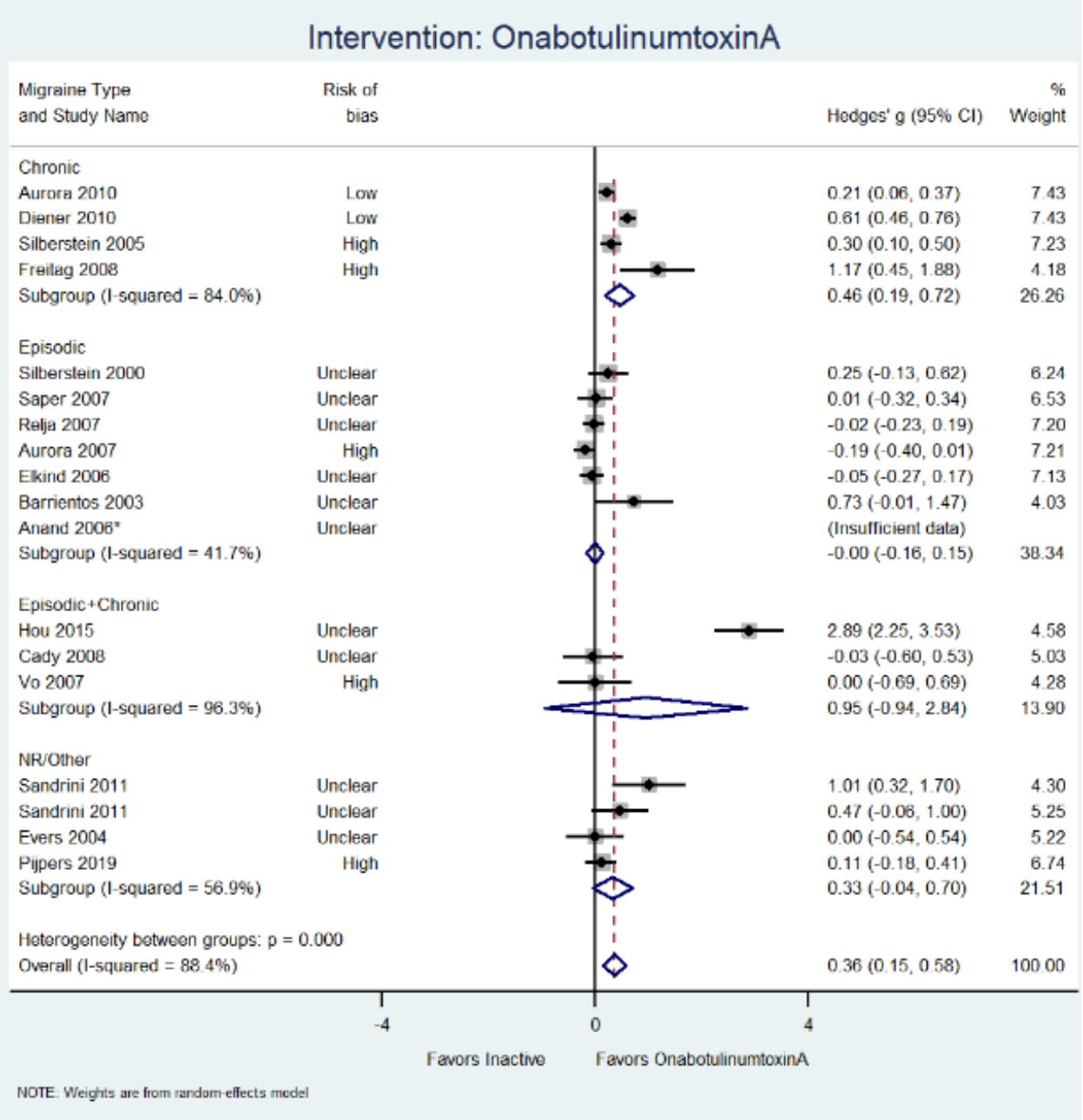


Figure E-12. Propranolol

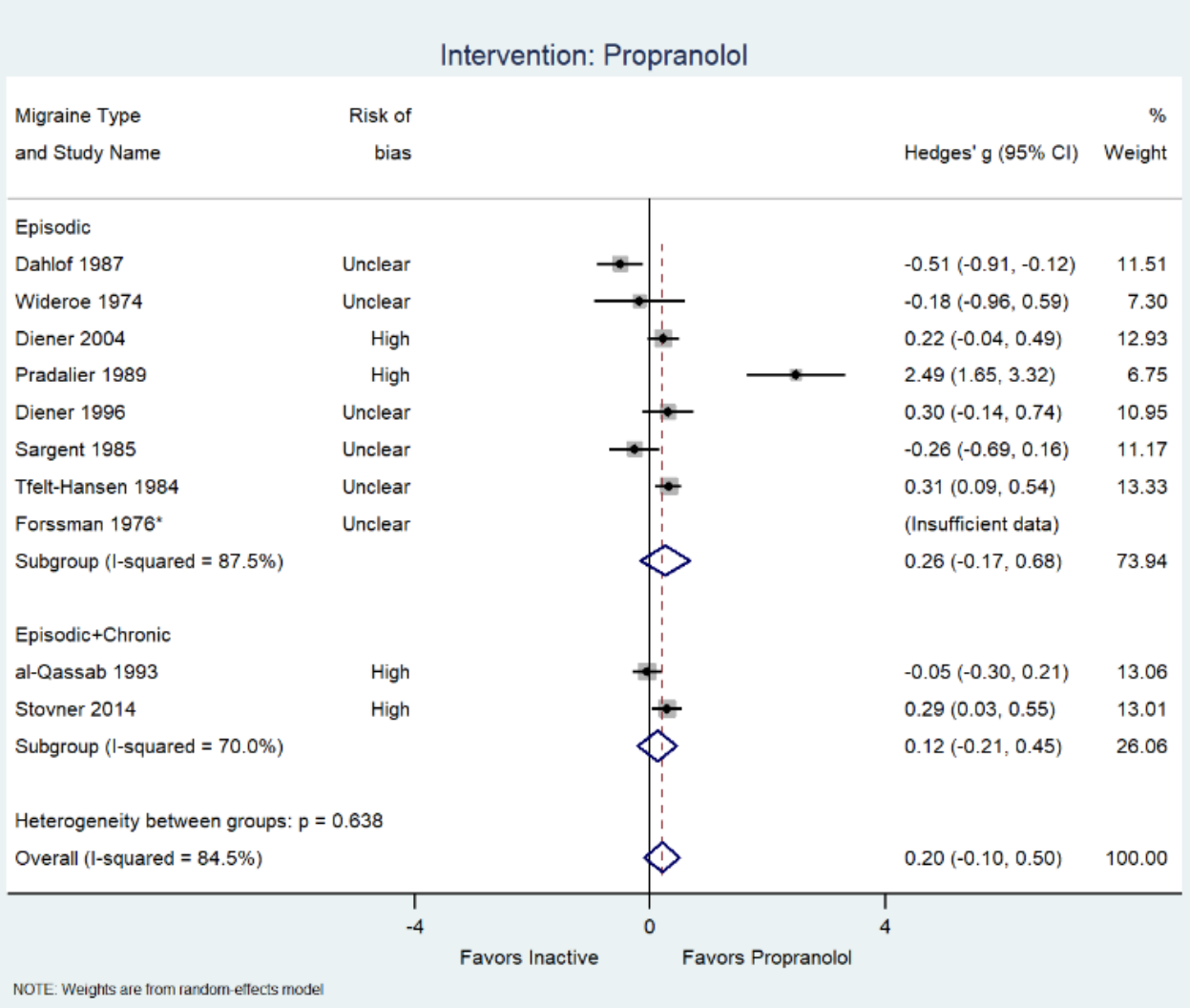


Figure E-13. Topiramate

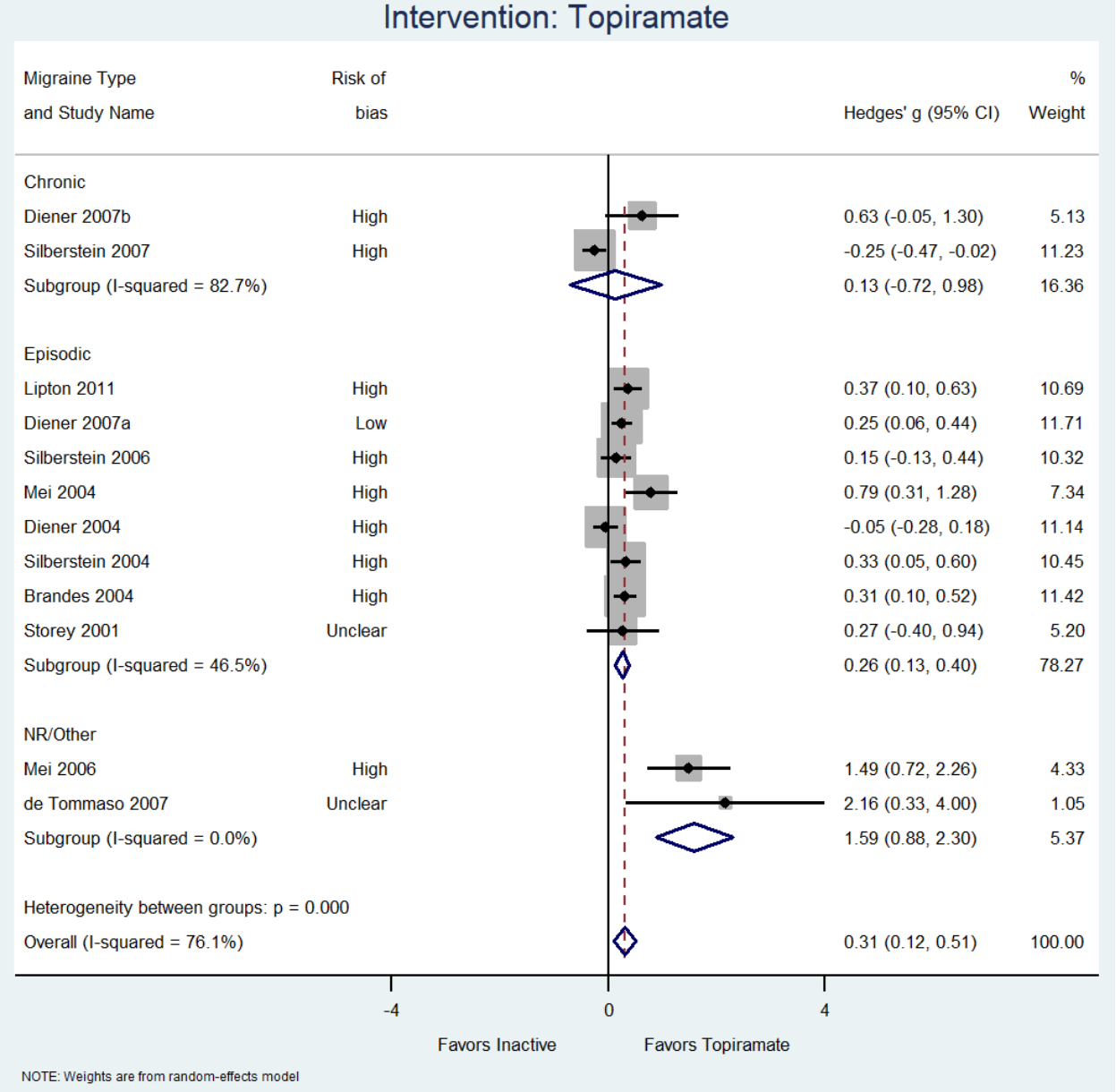


Figure E-14. Transcutaneous Supraorbital Nerve Stimulation

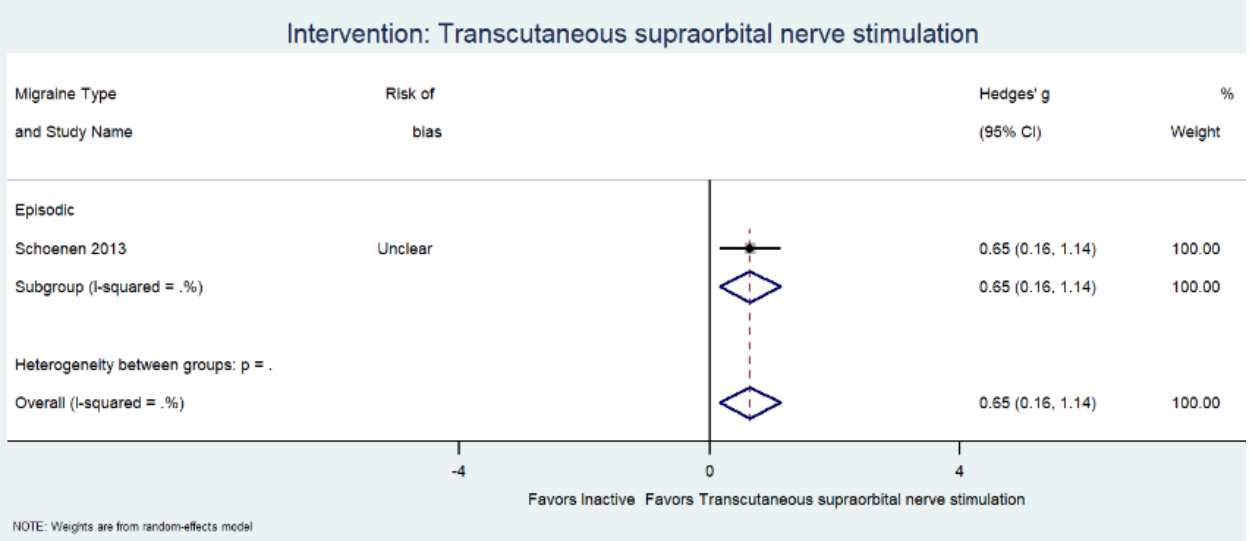


Figure E-15. Valproic Acid/Valproate

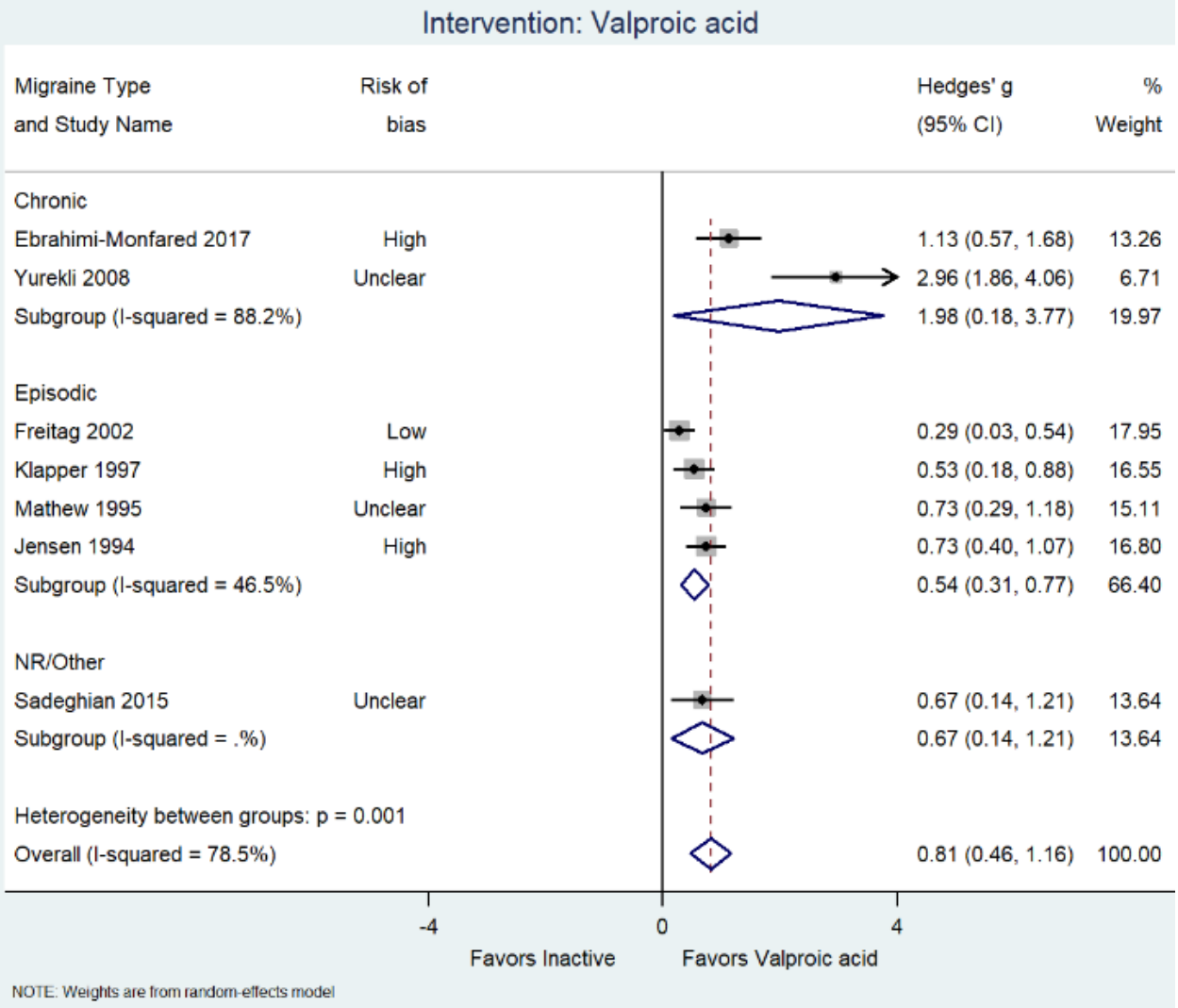
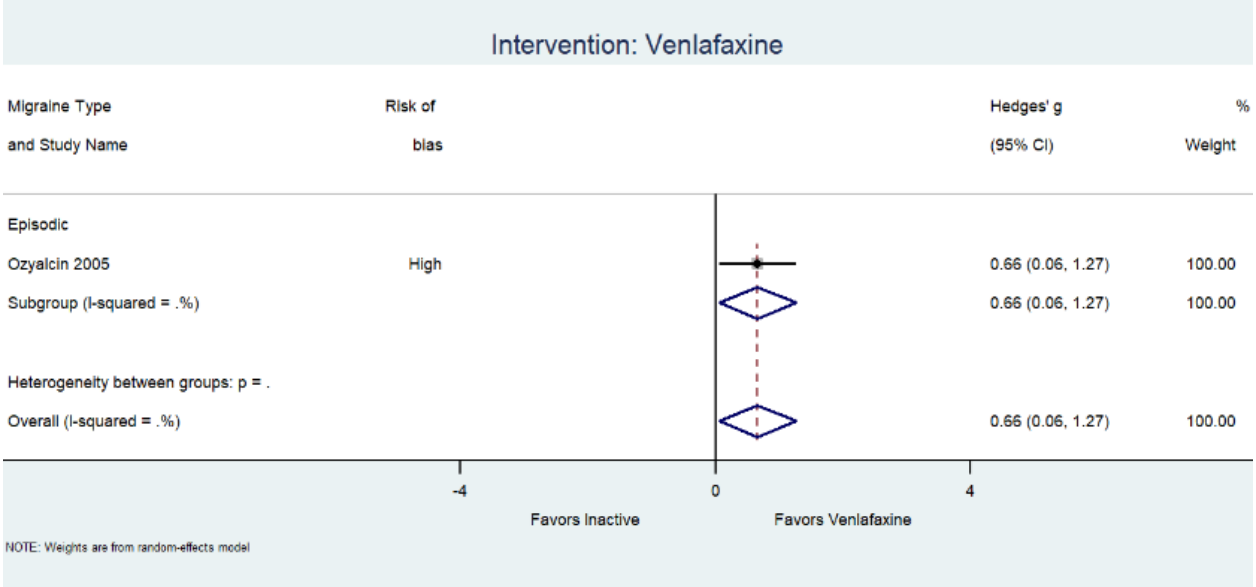


Figure E-16. Venlafaxine



Appendix F. Additional Data

Although we chose not to use 50% responder data as the key outcome for visualization of migraine reduction, for Map 1, these data were extracted from all included studies where available. Interventions for which 50% responder data were extracted are show in Table G-1.

Table F-1. Availability of 50% Reduction in Migraines per Month or Migraine Days per Month Data by Intervention

Intervention	Intervention Category	Data Available
Candesartan	Angiotensin Converting Enzyme (ACE) inhibitor/Angiotensin Receptor Blocker (ARB)	Yes
Lisinopril	ACE inhibitor/ARB	No
Topiramate	Antiepileptic	Yes
Valproate/valproic acid	Antiepileptic	Yes
Metoprolol	Beta-blocker	No
Propranolol	Beta-blocker	Yes
OnabotulinumtoxinA	Botulinum toxin type A	Yes
Atogepant	Calcitonin Gene Related Peptide (CGRP) antagonist	Yes
Eptinezumab	CGRP antagonist	Yes
Erenumab	CGRP antagonist	Yes
Fremanezumab	CGRP antagonist	Yes
Galcanezumab	CGRP antagonist	Yes
Noninvasive vagal nerve stimulation	Device	Yes
Transcutaneous supraorbital nerve stimulation	Device	Yes
Venlafaxine	Other antidepressant	No
Amitriptyline	Tricyclic antidepressant	Yes
Nortriptyline	Tricyclic antidepressant	No

Extracted data for each intervention (study name, migraine type, follow-up duration, risk difference, and relative risk) may be accessed using the visualization for Map 1. Users can view

these data by selecting a blue bar (under efficacy) and selecting the hyperlink for “Data on 50% reduction in migraines or migraine days per month” which appears in the hover.

Appendix G. Adverse Effects

For all studies that reported between group data for adverse effects, we calculated baseline risk, relative risk, pooled relative risk, and absolute risk difference using the following equations:

- Absolute risk difference = $|((baseline\ risk)x\ (relative\ risk - 1))|$
- Baseline risk = $\frac{total\ \#\ events\ in\ control\ group}{total\ \#\ people\ in\ control\ group}$
- Relative risk = $\frac{\frac{total\ no.events\ in\ intervention\ group}{total\ no.people\ in\ intervention\ group}}{\frac{total\ no.events\ in\ control\ group}{total\ no.people\ in\ control\ group}}$

Our 3-member technical expert panel (TEP) identified key adverse effects for each intervention (see Table F-1). We extracted data for each adverse effect (when reported by group) from each study. Absolute risk difference between intervention vs placebo/sham may be found in Map 1 by hovering over the orange dots for "adverse effects."

Table G-1. Key Adverse Events by Intervention

Intervention	Adverse Events (AEs) Identified for Extraction[a] (Additional Synonyms Extracted in Parentheses)	Number of Studies Reporting AE Data
Candesartan	Dizziness, hypotension, increased creatinine/impaired kidney function, lightheadedness, syncope (tendency to faint)	1
Lisinopril	Dizziness, hypotension, lightheadedness	1
Topiramate	Acute angle glaucoma, cognitive impairment (cognitive difficulties, difficulty with concentration/attention, difficulty with memory), decreased appetite (anorexia), kidney stones, paresthesias/tingling (distal paresthesias), teratogenicity, weight loss (slight weight loss), worsened mood (depression, emotional lability)	12
Valproate/valproic acid	Dizziness, fatigue (asthenia, tiredness), general adverse events, hair loss, liver problems, teratogenicity, tremor, weight gain	6
Metoprolol/propranolol	Bradycardia (low heart rate at exercise), dizziness, erectile dysfunction, exercise intolerance, fatigue (asthenia, tiredness), general adverse events, hypotension, lightheadedness, serious adverse events	Metoprolol—3 Propranolol—6

Intervention	Adverse Events (AEs) Identified for Extraction[a] (Additional Synonyms Extracted in Parentheses)	Number of Studies Reporting AE Data
OnabotulinumtoxinA	Difficulty breathing, double vision, eyelid droop (transient frontalis muscle asymmetry, upper eyelid ptosis), general adverse events, neck pain, neck weakness, serious adverse events, trouble swallowing/ dysphagia, worsened headache	15
Calcitonin Gene Related Peptide (CGRP) antagonists (atogepant, eptinezumab, erenumab, fremanezumab, galcanezumab)	Constipation, flulike symptoms, general adverse events, injection site reactions,[b] joint or muscle aches, new-onset hypertension, rhinorrhea, serious adverse events	Atogepant—1 Eptinezumab—3 Erenumab—6 Fremanezumab—5 Galcanezumab—7
Noninvasive vagus nerve stimulator (gammaCore)	Coughing or tickling (oropharyngeal pain), dizziness, tingling in neck	1
Transcutaneous supraorbital nerve stimulation (Cefaly)	Fatigue, paresthesias/tingling, worsened headache	1
Venlafaxine	Anxiety, constipation, dizziness, fatigue (asthenia, tiredness), hypertension, insomnia, nausea (gastric intolerance), weight gain, withdrawal syndrome, worsened mood	1
Amitriptyline/nortriptyline	Blurred vision, cardiac arrhythmia, constipation, dry eyes, dry mouth, nightmares, somnolence (drowsiness), tachycardia, urinary retention, weight gain	Amitriptyline—2 Nortriptyline—0

[a] Specified by 3 members of the TEP as key adverse effect for clinical decision making.
[b] If multiple adverse events at the injection site reported, most frequent adverse event was extracted.